

Steroid Allergy: Clinical Features and the Importance of Excipient Testing in a Diagnostic Algorithm



Philip H. Li, MRes(Med), MRCP^{a,b}, Annette Wagner, MD^c, Iason Thomas, MRCP^a, Timothy J. Watts, MRCP^a, Ryszard Rutkowski, MD, PhD^d, and Krzysztof Rutkowski, MD, MRCP^a *London and Cambridge, UK; Hong Kong; and Bialystok, Poland*

What is already known about this topic? True corticosteroid (CS) allergy is rare. Instead, some patients may be allergic to excipients found in various CS preparations. Excipient testing is frequently overlooked. It might lead to unnecessary CS avoidance or dangerous re-exposure.

What does this article add to our knowledge? Patients with respiratory manifestations were significantly more likely to be truly allergic. CS allergies are rare and the majority of patients are allergic to excipients.

How does this study impact current management guidelines? We propose a comprehensive diagnostic algorithm with excipient testing for suspected type I CS allergy and suggest the use of Carmellose eye drops as a readily available source of carboxymethylcellulose.

BACKGROUND: True corticosteroid (CS) allergy is rare. Instead, many patients may be allergic to excipients found in various CS preparations. Excipient testing is frequently overlooked. It might lead to unnecessary CS avoidance or dangerous re-exposure.

OBJECTIVE: The objective of this study was to evaluate the clinical characteristics and frequency of excipient allergy in patients with confirmed type I hypersensitivity to systemic CS preparations.

METHODS: Patients with a confirmed diagnosis of allergy (positive skin test or drug provocation test [DPT]) or tolerance (negative DPT to CS) over the past 10 years were studied. Patient characteristics, index CS, route of administration, clinical indications, symptoms of index reaction, and outcomes of CS/excipient allergy testing were analyzed.

RESULTS: Sixty-four patients underwent CS allergy testing. True CS allergy was confirmed in 9 of 64 (14%) patients. The majority (5/9, 56%) with positive skin tests or DPT were actually allergic to the excipients (2 to carboxymethylcellulose and 3 to polyethylene glycol) rather than the CS. Respiratory manifestations were significantly associated with confirmed allergy (odds ratio = 6.79 [95% confidence interval = 1.36-34.03], $P = .02$).

CONCLUSIONS: Patients with respiratory manifestations were significantly more likely to be truly allergic. CS allergies are rare and may be overdiagnosed without excipient testing. We suggest the use of Carmellose eye drops as a readily available source of carboxymethylcellulose for testing and propose a comprehensive diagnostic algorithm for suspected CS allergy. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1655-61)

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^aDepartment of Allergy, Guy's and St Thomas' NHS Foundation Trust, London, UK

^bDivision of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

^cDepartment of Allergy, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

^dDepartment of Respiratory Diagnostics, Medical University of Bialystok, Bialystok, Poland

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Corresponding author: Philip H. Li, MRes(Med), MRCP, Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, 102 Pokfulam Road, Hong Kong. E-mail: philipli@connect.hku.hk.

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Corticosteroids (CS) are synthetic analogs of the natural steroid hormones used to treat a wide range of inflammatory and autoimmune disorders in almost every field of medicine.¹ Despite their anti-inflammatory and immunosuppressive properties, both immediate (type I) and nonimmediate hypersensitivity reactions (HSR) have been reported. The estimated prevalence of immediate HSR is around 0.1% to 0.3%.²

CS are mainly administered systemically via the oral, intramuscular (IM), and intravenous (IV) route, but systemic effects after intra-articular (IA) and neuraxial injections have also been reported.^{3,4} IV, IM, and IA administration appear to be most commonly associated with CS-related type I HSR.⁵ Immediate HSR occur more frequently with systemic CS and can result in

Abbreviations used

CMC- Carboxymethylcellulose
 CS- Corticosteroid
 DPT- Drug provocation test
 HSR- Hypersensitivity reaction
 IA- Intra-articular
 IDT- Intradermal test
 IM- Intramuscular
 IV- Intravenous
 PEG- Polyethylene glycol
 SPT- Skin prick test
 ST- Skin testing

potentially life-threatening anaphylaxis.² In this paper, we regard all CS administered via these routes as “systemic CS.”

To date, the literature regarding confirmed cases of CS allergy has mostly been confined to isolated reports or small case series. Furthermore, there is growing evidence to suggest that many reactions are secondary to excipients found in systemic CS preparations, rather than the CS itself. Several systemic CS preparations are commercially available. They vary in their pharmacodynamics and pharmacokinetics and contain various combinations of excipients such as carboxymethylcellulose (CMC) and polyethylene glycol (PEG) both known to cause potentially fatal type I HSR.⁵ However, testing for potential excipient allergy is frequently overlooked. Patients are often mislabeled with CS allergy, leading to unnecessary avoidance or potentially dangerous exposure to other medications containing similar excipients. Larger studies to ascertain the prevalence of excipient allergy and well-designed protocols for more comprehensive evaluation are required.

In this retrospective study, we evaluate the clinical characteristics of patients with confirmed type I HSR to systemic CS and the importance of excipient testing. We report an increasing number of referrals for suspected allergy to methylprednisolone and triamcinolone that might be due to the National Institute for Health and Care Excellence recommendations to use these CS for medium or large joint injections.⁶ We also suggest a novel and more readily available source of CMC for excipient testing and propose a comprehensive diagnostic algorithm for suspected type I CS allergies.

METHODS

Collection of clinical data

The medical records of patients with suspected immediate-type CS HSR referred between 2008 and 2017 to Guy's and St Thomas' NHS Foundation Trust (London, UK) and Cambridge University Hospitals NHS Foundation Trust (Cambridge, UK) were reviewed. After detailed anamnesis, referred patients underwent allergy skin testing (ST: skin prick test [SPT] and intradermal test [IDT]) with the relevant CS preparations and excipients. Patients with negative ST were referred for drug provocation tests (DPT) with the index CS preparation. Case histories where the index CS (ie, the suspected CS implicated in the allergic reaction) was not known were excluded. Only patients with a confirmed diagnosis of allergy (either positive ST or DPT) or tolerance (negative DPT) were included. Those with negative ST but without confirmatory DPT were excluded.

Data extracted included sex and age; index CS, route of administration (IV, IM, IA, or oral), clinical use and symptoms of index

reaction; CS and excipient SPT/IDT results; and symptoms and outcomes of DPT. Clinical histories with delayed reactions or reactions to topical/inhaled CS were excluded. Allergy to other drugs given simultaneously during the index reaction, such as local anesthetics mixed with CS, was excluded with relevant DPT before CS allergy testing.

Patients were grouped depending on the clinical use of CS and route of administration: neuraxial (epidural, intrathecal, or perineural), musculoskeletal (IA or IM), perioperative (IV), other anti-inflammatory (oral or IV), or other/unknown history. Symptoms of index reactions were categorized based on the definition criteria for anaphylaxis into mucocutaneous (urticaria, pruritus, flushing, rash, angioedema), respiratory (dyspnoea, wheeze/bronchospasm, stridor, hypoxemia), gastrointestinal (nausea, vomiting, abdominal pain), hypotension, and others/unclassified.^{7,8}

CS formulations and their excipients

Common systemic CS preparations include dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and triamcinolone. According to the British National Formulary, many formulations of these different CS preparations are available. Methylprednisolone is available as methylprednisolone acetate (Depo-Medrone, Pfizer, Surrey, UK), methylprednisolone sodium succinate (Solu-Medrone, Pfizer), or methylprednisolone tablets (Medrone, Pfizer). Depo-Medrone contains PEG and myristyl-gamma-picolinium chloride; the 40 mg/mL formulation of Solu-Medrone contains lactose. Triamcinolone is available as triamcinolone acetonide (Adcortyl and Kenalog, Bristol-Myers Squibb Pharmaceuticals, Middlesex, UK; Triesence, Alcon Laboratories, UK) or triamcinolone hexacetonide (Intrapharm, Berkshire, UK). Adcortyl, Kenalog, and Triesence contain CMC and polysorbate 80. Triamcinolone hexacetonide contains sorbitol (E420) and polysorbate 80.

Allergy testing

Patients underwent ST (both SPT and IDT) with the same CS compound implicated in the index reaction in addition to the relevant excipient testing (depending on the index CS). DPT were performed to confirm or refute negative ST results, or to identify a suitable alternative CS. SPT or IDT were considered positive if wheal size or wheal expansion was >3 mm at 20 minutes, respectively. Sodium chloride 0.9% and histamine dihydrochloride at 10 mg/mL (ALK Therapeutics, Hørsholm, Denmark) were used as negative and positive controls, respectively.

SPT were performed with stock solutions and IDT with 1:10 dilutions of CS in 0.9% sodium chloride. The SPT and IDT concentrations and the CS manufacturers were as follows: dexamethasone (4 and 0.4 mg/mL; Hameln Pharmaceuticals Ltd, Gloucester, UK), hydrocortisone sodium succinate (50 and 0.5 mg/mL; Pfizer), methylprednisolone acetate (40 and 4 mg/mL), methylprednisolone sodium succinate (40 and 4 mg/mL), and triamcinolone acetonide (40 and 4 mg/mL). SPT with PEG was performed with Movicol (PEG 3350; Norgine Limited, Harefield, UK), diluted to 105 mg/mL of PEG 3350 as per the manufacturer's instructions. These were known nonirritating concentrations as corroborated by other reports and our long-term clinical practice including testing on healthy volunteers as well as patients exposed to CS during a confirmed reaction to non-CS drugs.^{9,10} SPT and IDT with CMC were performed with preservative free Carmellose eye drops 1% (Moorfields Pharmaceuticals, London, UK) with undiluted and 1:10 dilution, respectively. These concentrations for ST with CMC were confirmed to be nonirritant in 8 nonallergic controls.

DPT protocols were tailored to the individual patients and adjusted depending on risk assessment. All patients were administered the same CS and the same formulation implicated in the index reaction in a graded fashion. DPT were considered positive if objective signs suggestive of an IgE-mediated response developed: acute rash/urticaria, angioedema, and wheeze; drop in peak expiratory flow rate, oxygen saturation, or blood pressure. The study was a retrospective review and all patients received the usual standard of care.

Statistical analysis

Association analysis was performed to study variables associated with a diagnosis of CS allergy. Categorical variables were expressed as number (percentage) and continuous variables as mean (standard deviation) when appropriate. Fisher's exact test and independent samples *t*-test were used to compare categorical and continuous variables between groups in univariate analysis, respectively. Variables with a *P* value $\leq .1$ from univariate analysis were included in multivariate logistic analysis to determine which variables were independent predictors of allergy. A *P* value $< .05$ was considered statistically significant. SPSS Statistics version 20 (IBM Corporation, Armonk, NY) was used for all analyses.

RESULTS

Patient demographics and clinical features

Overall, a total of 64 patients were referred and underwent investigations for suspected type I HSR to CS preparations. The demographics, clinical indication, route of administration, and symptoms of index reaction of all allergic and nonallergic patients are listed in Table I. "Other anti-inflammatory" clinical indications included treatment for asthma (*n* = 7), chronic obstructive pulmonary disease (*n* = 4), adjunct treatment for infections (*n* = 2), inflammatory arthritis (*n* = 1), inflammatory bowel disease (*n* = 1), inflammatory myositis (*n* = 1), and systemic lupus erythematosus (*n* = 1). Overall, patients were generally middle-aged (median: 57 years, range: 27-87 years) and mostly female (M:F ratio = 1:3). Of the total 64 patients, the index drugs were prednisolone- (*n* = 18, 28.1%), triamcinolone- (*n* = 17, 26.6%), methylprednisolone- (*n* = 17, 26.6%), dexamethasone- (*n* = 7, 10.9%), and hydrocortisone-containing preparations (*n* = 5, 7.8%). All patients had been avoiding all formulations of CS since their index reaction.

Respiratory manifestations significantly associated with confirmed allergy

Univariate association analysis revealed that cardiovascular (*P* = .03) and respiratory (*P* = .01) manifestations during the index reaction were significantly more likely in allergic than nonallergic patients. However, only respiratory manifestations (odds ratio = 6.79 [95% confidence interval = 1.36-34.03], *P* = .02) remained statistically significant after multivariate logistic regression. Otherwise there were no significant differences between allergic and nonallergic in the other studied variables (*P* > .05).

True CS allergy was rare but often due to excipient allergy

Allergy was excluded in 55 of 64 patients (negative DPT with the index CS). Based on either positive ST or DPT, type I HSR to CS preparations was confirmed in 9 of 64 (14%) patients. The clinical features, investigation results, and final diagnoses of the confirmed allergic patients are summarized in Table II. Despite

repeated attempts of calling patients back for further testing, not all completed a full diagnostic workup with excipient testing and/or DPT with suitable CS alternatives. Two-thirds (6/9) of patients were allergic to triamcinolone-containing preparations, of whom 2 were confirmed to have CMC allergy by ST. Four patients with allergy to triamcinolone-containing preparations had incomplete evaluations. The remaining 3 of 9 allergic patients were confirmed to have allergy to methylprednisolone-containing preparations due to PEG allergy. Patient 3 was diagnosed with PEG allergy by a positive DPT to Depo-Medrone (methylprednisolone acetate with PEG), but tolerated Solu-Medrone (PEG-free methylprednisolone sodium succinate). Although there is a theoretical risk of an isolated acetate allergy, ST with PEG was not available during initial allergy workup and the patient declined to return for repeat testing.

No patients were found to be allergic to other CS preparations tested: prednisolone, dexamethasone, and hydrocortisone.

DISCUSSION

We present the largest published cohort of patients with suspected CS allergy investigated with DPT. A previous review found a total of only 106 patients with immediate-type reactions between 2004 and 2014.⁵

True immediate HSR were found in only 14% of all referred patients via either positive skin tests or DPT. The majority of confirmed cases had a history of multisystem involvement/anaphylaxis during their index reactions. This highlights the importance of accurate and specific (ie, CS vs excipient) diagnosis. Furthermore, we identified that patients with confirmed type I allergy were more likely to present with a history of respiratory manifestations (dyspnoea, wheeze, stridor, or hypoxemia) during their index reaction than nonallergic patients. We therefore suggest cautious evaluation when patients with suspected type I HSR to CS preparations present a history of respiratory involvement during their index reaction. Although methylprednisolone, prednisolone, and triamcinolone were the most commonly suspected index drugs in the referrals received by our centers over the past 10 years, a genuine allergy was confirmed only to methylprednisolone- and triamcinolone-containing preparations.

In our cohort, the majority of patients with positive skin tests or DPT to various CS preparations were actually allergic to the excipients rather than the CS. It is important to note that many previous reports of CS allergy reported no testing for potential excipient allergy. We therefore propose that CS allergy may have been overdiagnosed because of omission of testing for excipient allergy. This could have serious implications including unnecessary CS avoidance or inadvertent exposure to other excipient-containing preparations in the future. Specifically, all our patients with confirmed allergy to methylprednisolone acetate (Depo-Medrone) were allergic to the PEG excipient rather than the methylprednisolone component. This was confirmed by subsequent negative DPT with the PEG-free methylprednisolone sodium succinate (Solu-Medrone) and positive skin tests to PEG. Interestingly, we have not identified any patients with true methylprednisolone allergy. PEG (also known as macrogol) is a hydrophilic polyether frequently used as a surfactant, dispersing agents, and as the basis of several laxatives. If PEG allergy is still suspected despite initial negative SPT, we suggest further testing with a range of PEG dilutions and molecular weights.¹⁰ Systemic reactions have been

TABLE I. Demographics, clinical indication/route of administration, and symptoms of index reactions in confirmed allergic and nonallergic patients

Parameters	Total n = 64	Allergic n = 9	Nonallergic n = 55
Demographics			
Age, median (range)	57 (27-87)	60 (42-82)	55 (27-87)
Male	15 (23.4%)	2 (22.2%)	13 (23.6%)
Clinical indication/route of administration			
Musculoskeletal (intra-articular or intramuscular)	29 (45.3%)	7 (77.8%)	22 (40.0%)
Other anti-inflammatory (oral or intravenous)	17 (26.6%)	0	17 (30.9%)
Neuraxial (epidural, intrathecal, or perineural)	7 (10.9%)	2 (22.2%)	5 (9.1%)
Perioperative (intravenous)	4 (6.3%)	0	4 (7.3%)
Unknown	7 (10.9%)	0	7 (12.7%)
Index reactions			
Mucocutaneous (urticaria, pruritus, flushing, rash, angioedema)	47 (73.4%)	5 (55.6%)	42 (76.4%)
Respiratory (dyspnoea, wheeze, stridor, hypoxemia)	12 (18.8%)	5 (55.6%)*	7 (12.7%)*
Cardiovascular (hypotension, dizziness, pre-syncope, syncope)	10 (15.6%)	4 (44.4%)	6 (10.9%)
Gastrointestinal (nausea, vomiting, abdominal pain)	3 (4.7%)	2 (22.2%)	1 (1.8%)
Unknown	2 (3.1%)	0	2 (3.6%)
Index corticosteroid preparations			
Prednisolone	18 (28.1%)	0	18 (32.7%)
Triamcinolone	17 (26.6%)	6 (66.7%)	11 (20%)
Methylprednisolone	17 (26.6%)	3 (33.3%)	14 (25.5%)
Dexamethasone	7 (10.9%)	0	7 (12.7%)
Hydrocortisone	5 (7.8%)	0	5 (9.1%)

*Significantly more likely in allergic than nonallergic patients (odds ratio = 6.79 [95% confidence interval = 1.36-34.03], $P = .02$).

reported with PEG IDT and oral DPT. We therefore recommend that IDT or DPT should be performed cautiously when there is diagnostic uncertainty in SPT-negative patients.^{10,11}

Similarly, at least 2 of 6 of patients with confirmed allergy to triamcinolone acetonide (Kenalog and Adcortyl) had CMC allergy, confirmed by positive CMC ST. CMC (also known as Carmellose, E466) is a hydrophilic derivative of cellulose and is often used as a suspending agent to promote solubilization and as a lubricant. Allergy to CMC has been reported, including in triamcinolone-containing injections.^{5,12} Unfortunately, excipient allergy could not be excluded in the remaining 4 of 6 patients because of the unavailability of excipient testing reagents at our centers in the past and patients' reluctance to attend additional excipient testing. In response to this deficit, we identified Carmellose eye drops as a readily available source of CMC for both SPT and IDT. We have since successfully diagnosed cases of CMC allergy with positive ST after incorporating CMC into our routine testing panel.

It is important to note that oral CMC is poorly absorbed through the digestive tract. It is tolerated by patients allergic to systemically administered (injectable) CMC (false negative results).^{12,13} After CMC ST, we strongly recommend further testing with excipient-free triamcinolone instead. This preparation was previously unavailable in our centers and we were unable to determine if 2 patients with confirmed Kenalog allergies (patients 6 and 7 in Table II) had a genuine triamcinolone and/or excipient allergy (ie, false negative CMC skin tests). Without further evaluation, the predictive value of CMC skin tests remains to be elucidated.

We propose a comprehensive diagnostic algorithm for suspected type I hypersensitivity to various CS-containing preparations (Figure 1). We include the possibility of an allergy to milk

protein-contaminated lactose contained exclusively in the 40 mg/mL Solu-Medrone formulation as well as to the succinate ester of methylprednisolone that have been previously reported.¹⁴⁻¹⁹ In the context of CS-related allergy, we are unaware of other previous convincing reports of confirmed type I HSR to other excipients such as benzyl alcohol, E420, polysorbate 80, and myristyl-gamma-picolinium chloride; they were therefore not included in the algorithm. However, further testing with these excipients can be considered on a case-by-case basis if there is a compatible clinical history and all other tests remain negative. Subsequent to this study, the rate of complete allergy testing in new referrals has substantially improved since the implementation of this comprehensive diagnostic algorithm.

All CS-allergic patients should be thoroughly counseled and, in the case of excipient allergy, provided a list of common excipient-containing preparations. It is also important to provide all patients with confirmed allergy with a suitable alternative: an excipient-free formulation or a different CS depending on the patient's diagnosis. Unlike in delayed-type allergy, the Coopman classification does not seem to apply to type I HSR and there seems to be very little cross-reactivity.²⁰ However, in view of the scarcity of data, a confirmatory graded DPT with an alternative CS is recommended.

The main limitations of this study stem from the limitation of the medical records review. The data on comorbidities (including asthmatic status), acute or basal tryptase levels, or the delay between the index reaction and testing were not available. Furthermore, our diagnostic algorithm and full excipient testing panel was not consistently available throughout the entire study period. Although patients were called back to complete testing afterward, almost a third of confirmed allergic patients (positive ST or DPT) declined to return for completion of their allergy

TABLE II. Clinical features, investigation results, and final diagnoses of 9 confirmed allergic patients

	Sex/age	Index drug	Index reaction	Skin test	DPT outcome with index drug	Suitable alternative CS (negative DPT)	Final diagnosis
1	M/66	Triamcinolone acetonide (Kenalog)	Epidural injection for chronic back pain. Developed respiratory arrest	Kenalog(+), CMC(+)	Not performed because of positive skin test	Patient declined	CMC allergy
2	F/80	Triamcinolone acetonide (Kenalog)	Sacroiliac joint injection. Developed dyspnoea, generalized urticaria, and syncope (unrecordable SBP)	Kenalog(+), CMC(+)	Not performed because of positive skin test	Methylprednisolone acetate	CMC allergy
3	F/42	Methylprednisolone acetate (Depo-Medrone)	Nausea and vomiting, with urticaria few minutes after shoulder intra-articular injection	Depo-Medrone(−), Solu-Medrone(−)	Erythema/pruritus over limbs with nasal irritation and throat tightness	Methylprednisolone sodium succinate	PEG allergy
4	M/42	Methylprednisolone acetate (Depo-Medrone)	Difficulty in breathing 30 min after shoulder intra-articular injection	Depo-Medrone(−), Solu-Medrone(−), PEG(+) [†]	Urticaria over abdomen and lower limbs	Methylprednisolone sodium succinate	PEG allergy
5	F/52	Methylprednisolone acetate (Depo-Medrone)	Nausea, difficulty in breathing, and hypotension after injection into the thumb	Depo-Medrone(−), Solu-Medrone(−), PEG(+) [†]	Generalized pruritus and flushing with dizziness	Patient declined	PEG allergy
6*	F/60*	Triamcinolone acetonide (Kenalog)	Epidural injection for chronic back pain. Immediate facial angioedema and urticaria during procedure	Kenalog(−), CMC(−)	Generalized urticaria	Patient declined	Kenalog allergy, incomplete workup
7*	F/80*	Triamcinolone acetonide (Kenalog)	Local injection for back pain. Felt dizzy and found hypotensive after injection	Kenalog(+), CMC(−)	Not performed because of positive skin test	Patient declined	Kenalog allergy, incomplete workup
8*	F/82*	Triamcinolone acetonide (Kenalog)	Lumbar facet joint injection. Generalized pruritus followed by syncope (SBP 77 mm Hg)	Kenalog(−)	Generalized unwell with tremor and widespread urticaria. Required hospitalization	Hydrocortisone	Kenalog allergy, incomplete workup
9*	F/58*	Triamcinolone acetonide (Adcortyl)	Generalized urticaria and chest tightness 30 min after intra-articular knee injection	Adcortyl(+)	Not performed because of positive skin test	Methylprednisolone acetate	Adcortyl allergy, incomplete workup

CMC, Carboxymethylcellulose; CS, corticosteroids; DPT, drug provocation test; PEG, polyethylene glycol; SBP, systolic blood pressure.

*Patients declined invitations for further testing.

[†]PEG skin tests were performed during patients' subsequent visit, that is, after previously positive DPT.

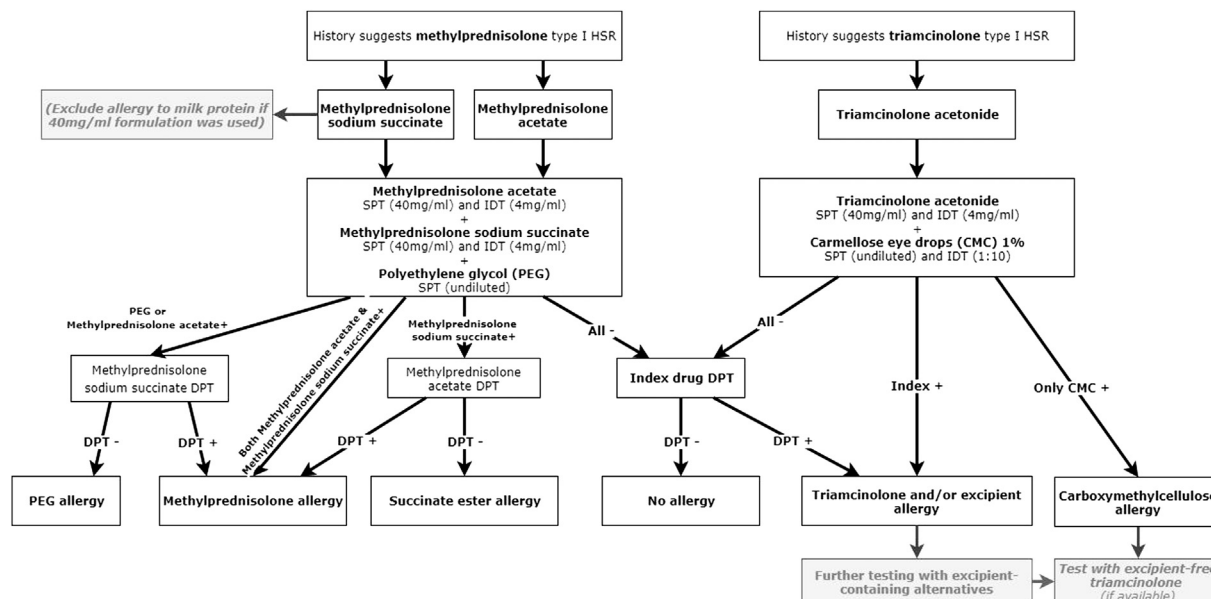


FIGURE 1. Diagnostic algorithm for suspected corticosteroid type I HSR. CMC, Carboxymethylcellulose; DPT, drug provocation test; HSR, hypersensitivity reactions; IDT, intradermal test; SPT, skin prick test.

testing. The unavailability of the excipient-free triamcinolone preparation did not allow for differentiation between true triamcinolone and/or excipient allergy. Our results should be interpreted in the context of different excipients in CS formulations available in different countries. We would encourage further studies to confirm the predictive value of CMC ST, especially using suggested Carmellose eye drops as well as prospective studies to evaluate this new comprehensive diagnostic algorithm. Further research into potential utility of *in vitro* tests such as basophil activation tests in excipient testing would also be of great interest.²¹

CONCLUSIONS

We report on the clinical characteristics and outcomes of allergy testing in the largest cohort of patients with suspected type I allergy to CS preparations reported thus far. Patients who experienced respiratory manifestations during their index reaction were significantly more likely to be truly allergic. True allergy to CS preparations was rare and the majority of confirmed cases were actually allergic to excipients. We hypothesize that CS allergy may be overdiagnosed in the past. We highlight the importance of excipient testing and suggest Carmellose eye drops as a readily available source of CMC for testing. We believe that our comprehensive diagnostic algorithm will facilitate the diagnosis of true CS allergy.

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PHL, AW, IT, and TJW collected the data. PHL, AW, RR, and KR analyzed and interpreted the data. All authors contributed in the writing and revision of the article.

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