

Immediate and Delayed Hypersensitivity Reactions to Corticosteroids: Evaluation and Management

Iris M. Otani¹ · Aleena Banerji¹

© Springer Science+Business Media New York 2016

Abstract Corticosteroids are anti-inflammatory medications used widely to treat allergic inflammation. Although the endocrine and gastrointestinal side effects of corticosteroids have been described, the occurrence of immediate hypersensitivity reactions and delayed contact dermatitis due to corticosteroids remains under-recognized. Hypersensitivity reactions can occur to a corticosteroid itself, or to the additives and vehicles in corticosteroid preparations. Skin testing and oral graded challenge can help confirm the suspected culprit agent in immediate hypersensitivity reactions and help identify an alternative tolerated corticosteroid. Patch testing can help identify the culprit agents in delayed hypersensitivity contact dermatitis. Cross-reactivity patterns have not been observed for immediate hypersensitivity reactions as they have been for delayed contact dermatitis. Sensitization in contact dermatitis exhibits cross-reactivity patterns based on corticosteroid structure. We review the current understanding regarding the clinical presentation, evaluation, and management of immediate and delayed hypersensitivity reactions to corticosteroids.

Keywords Drug allergy · Hypersensitivity reaction · Adverse drug reaction · Corticosteroids · Allergic contact dermatitis · Skin testing

Introduction

Corticosteroids are widely used for their anti-inflammatory effects [1]. As corticosteroids are often used to treat allergic reactions, they can be overlooked as a cause of immune-mediated hypersensitivity reactions. However, allergic reactions to corticosteroids have been reported with an estimated prevalence of 0.1 to 0.3 % [2]. Delayed reactions to topical corticosteroids have been reported with a higher frequency of 0.5 to 5 % [3]. This review summarizes our current understanding of the clinical presentation, diagnostic evaluation, and management of immune-mediated hypersensitivity reactions to corticosteroids.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions to corticosteroids have been reported across a wide range of ages (2 to 90 years of age) with similar prevalence between genders [4•]. Two reviews, spanning from 1966 to 1997 and 2004 to 2014, identified 174 reported cases of immediate hypersensitivity reactions to corticosteroids in the literature [4•, 5]. Anaphylaxis (most frequently involving urticaria, angioedema, bronchospasm, vomiting, cardiovascular collapse) is the most commonly reported presentation, followed by isolated urticaria or bronchospasm [4•].

The most commonly implicated corticosteroid is methylprednisolone (41 % of cases), followed by prednisolone (20 %), triamcinolone (14 %), and hydrocortisone (10 %)

This article is part of the Topical Collection on *Anaphylaxis and Drug Allergy*

✉ Iris M. Otani
iotani@mgh.harvard.edu

Aleena Banerji
abanerji@mgh.harvard.edu

¹ Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA, USA

[4••]. Reactions occur most commonly following intravenous administration (44 % of cases), followed by oral (26 %) administration [4••, 5]. Reactions following intra-articular, ophthalmic, and topical corticosteroids have been reported as well [4••, 5, 6••]. One case of an immediate hypersensitivity reaction following inhaled corticosteroid was found to be a reaction to the lactose additive [7].

The majority of immediate hypersensitivity reactions occur within an hour of administration [4••, 5]. Reported cases of anaphylaxis and fatalities all occurred within the first hour after steroid administration [4••, 5, 8–11]. Although fatal reactions attributed to steroids have been reported up to 11 to 17.5 h after steroid administration [12], it remains inconclusive whether these mortalities were adverse effects of steroid administration or sequelae of significant underlying medical comorbidities.

Pathophysiology of Immediate Hypersensitivity Reactions to Corticosteroids

A variety of possible mechanisms for immediate reactions to corticosteroids have been proposed. Given the nature of the symptoms (pruritus, urticaria, angioedema, bronchospasm), mast cell-mediated mechanisms are likely responsible for some immediate hypersensitivity reactions. It is thought that serum-specific IgE for the culprit corticosteroid is rarely identified due to the fact that haptenization is necessary for corticosteroids to elicit an allergic response [5, 6••, 13]. Cyclooxygenase inhibition akin to aspirin-mediated sensitivity has also been raised as a possible mechanism accounting for paradoxical bronchospasm and worsening of asthma seen after steroid administration [14–22]. It has been suggested that fatal reactions are due to cardiovascular collapse resulting from direct effects of corticosteroids on cardiac or smooth muscle or changes in ion concentrations affecting myocardial function [9, 23], although this effect has not been reproducible in humans [10].

Immediate reactions following corticosteroid administration can also be due to sensitization to additives in the corticosteroid preparations, rather than the actual corticosteroid molecule itself. The pathophysiology of corticosteroid-induced contact dermatitis is discussed later in this review.

Corticosteroid Structure and Cross-Reactivity

The Coopman classification categorizes corticosteroids in four reactivity groups (A, B, C, and D) based on their structural and clinical characteristics [24]. While cross-reactivity patterns between structurally similar corticosteroids have been established for delayed reactions (contact dermatitis) [25], similar cross-reactivity patterns have not been established for immediate hypersensitivity reactions. Alternative corticosteroids in the same group as the culprit corticosteroids are often

tolerated, and cross-reactivity between corticosteroids in differing chemical groups have been observed [26–28]. Therefore, there is no evidence to suggest that corticosteroids in the same chemical group as the culprit corticosteroid should be discounted as a possible alternative agent. Skin testing and graded challenge can be used to help identify an alternative, tolerated corticosteroid [4••, 5].

Diagnostic Testing

Skin prick and intradermal testing performed at non-irritating concentrations of corticosteroids can be useful in evaluating immediate hypersensitivity reactions. Serum-specific IgE is not a reliable measure of corticosteroid allergy, as mentioned earlier [5, 13].

Prior publications have reported that skin prick or intradermal testing at non-irritating concentrations was positive following a suspected immediate hypersensitivity reaction to corticosteroid in the majority of cases (73/105) [4••, 5]. It is important to include intradermal testing in the evaluation, as intradermal testing likely increases sensitivity of testing. Among 80 cases reported in Patel et al., 25 had negative skin prick testing followed by positive intradermal testing to the suspected corticosteroid [4••]. However, a retrospective review of the reported cases suggests that the sensitivity of intradermal testing is still low [6••, 28–34]. Out of eight positive drug challenges identified in the literature, three were preceded by a positive intradermal test and five were preceded by a negative intradermal test [6••, 28–34].

Intradermal testing appears to be most helpful in identifying alternative corticosteroid agents that will be tolerated. Out of 36 negative corticosteroid challenges performed with alternative corticosteroid agents, all were preceded by negative intradermal tests [5, 27, 28, 30–32, 34–38]. Retrospective review of the reported cases (including reports of intradermal testing followed by drug challenge performed with initially implicated corticosteroids as well as alternative corticosteroids) suggests that negative predictive value and specificity is high (88 and 97 %, respectively) [5, 6••, 26–28, 30–32, 34–38].

Our interpretation of these reports is limited as testing between case reports was not standardized or consistently confirmed by drug challenge. Large systematic studies of skin prick and intradermal testing performed with non-irritating concentrations of corticosteroids are needed to validate predictive values.

Chemical Modification with Esters

Succinate Ester

Corticosteroids are combined with esters at the C21 position to increase their solubility [39]. Succinate is the most common

ester used for intravenous therapy [5] and can be responsible for roughly one tenth of reported reactions to intravenous corticosteroids [4•, 26, 33, 37, 40–44]. Sodium phosphate and acetate esters can only be used for intra-articular or soft tissue administration [5], and hypersensitivity to these esters have not been reported. The succinate ester moiety has been proposed to somehow increase the sensitizing potential of corticosteroids, although the mechanism is unclear [44]. It is possible that initially proposed cross-reactivity patterns were due to sensitivity to the succinate ester used to solubilize group A corticosteroids (methylprednisolone, prednisolone, hydrocortisone) for intravenous administration [26, 44].

For patients who present with suspected immediate hypersensitivity reactions to succinated corticosteroids, evaluation for both the succinate form and unconjugated form of steroids (for example, methylprednisolone succinate and methylprednisolone) should be performed to differentiate between corticosteroid and succinate ester hypersensitivity.

Additives

Sensitization can also occur to additives in corticosteroid preparations. Hypersensitivity reactions to additives account for roughly one fifth of immediate hypersensitivity cases reported to corticosteroid preparations [4•]. Sensitivities to lactose [7, 45–47], carboxymethylcellulose [26, 48–52], polyethylene glycol [53–56], and hexylene glycol [57] (listed in order of decreasing frequency) have been reported.

Lactose

Ten cases of milk-allergic individuals developing anaphylaxis (8/10) or urticaria (2/10) after receiving lactose-containing corticosteroid preparations have been reported [7, 45–47]. Reactions occurring to lactose additives seen in milk-allergic children are due to IgE-mediated sensitization to milk [7, 45–47]. The corticosteroid preparations implicated were inhaled fluticasone and salmeterol (Advair) in one case and methylprednisolone succinate in nine cases. Caution should be exercised when administering corticosteroids in milk-allergic individuals [58].

Carboxymethylcellulose

Carboxymethylcellulose sensitivity has been reported with intralesional and intra-articular injection of triamcinolone [26, 48–52]. Carboxymethylcellulose is an osmotically active ingredient that is used as a suspension agent in parenteral preparations and a solubilizing or bulking agent in cosmetics, medications, and barium sulfate radiocontrast media [26, 59, 60]. Little is known regarding the mechanism of hypersensitivity to carboxymethylcellulose. One could conjecture that carboxymethylcellulose, as an osmotically active agent,

causes direct mast cell activation upon intravenous administration of the agent, akin to reactions seen with hyperosmolar radiocontrast media. Indeed, it has been reported that patients with hypersensitivity reactions after local injections of carboxymethylcellulose tolerate oral challenge with carboxymethylcellulose, suggesting that route of administration may play a role in precipitating reactions [60]. However, anaphylaxis following orally administered carboxymethylcellulose has been reported, and oral radiocontrast media containing carboxymethylcellulose should be avoided in sensitized patients [59].

Polyethylene Glycol

Macrogols are ethylene glycol polymers (PEG) used in food and cosmetics that are also used as pharmaceutical additives. Although sensitization is less commonly reported compared to previously listed additives, it should still be considered as a possible culprit if listed in the ingredients [53–56].

Conclusions and Recommendations for Immediate Hypersensitivity Reactions

- Immediate hypersensitivity reactions are rare but have been reported with an incidence of 0.3 to 0.5 % [2].
- Suspicion should be raised for IgE-mediated hypersensitivity to corticosteroids in patients who develop allergic-type reactions within 1 hour after corticosteroid administration.
- Evaluation should consist of skin prick and intradermal testing performed with non-irritating concentrations of corticosteroids. At our institution, we have been using the previously reported non-irritating concentrations listed in Table 1.
- For patients who present with suspected immediate hypersensitivity reactions to esterified corticosteroids, evaluation for both the succinate form and unconjugated form of the corticosteroid (for example, methylprednisolone succinate and methylprednisolone) should be performed to differentiate between corticosteroid and succinate ester hypersensitivity.
- When appropriate, evaluation should consist of skin prick and intradermal testing for additives including milk proteins, carboxymethylcellulose, and polyethylene glycol.
- Results of negative intradermal testing should be confirmed with drug challenge.

Contact Dermatitis

Contact dermatitis has been reported with a higher frequency of 0.5 to 5 % compared to immediate hypersensitivity reactions [3, 25, 65•]. While contact dermatitis does not have the

Table 1 Recommended immediate hypersensitivity testing for corticosteroids and excipients. Dilutions adapted from listed references [6•, 26, 28, 54, 61–64]

Corticosteroid	Skin prick test dilutions (mg/mL)	Intradermal tests dilutions (mg/mL)	References
Betamethasone sodium phosphate	4	4	Asakawa et al., Figueredo et al., Venturini et al., Figueredo et al.
Betamethasone acetate	6	6	Mace et al., Montoro et al.
Budesonide	0.25	0.0025 0.025	Venturini et al.
Dexamethasone sodium phosphate	4	0.04 0.4 4	Mace et al., Venturini et al., Rachid et al., Baker et al.
Hydrocortisone sodium succinate	100	1 10 25	Figueredo et al., Rachid et al., Venturini et al., Montoro et al.
Methylprednisolone acetate	40	0.4 4	Mace et al., Venturini et al., Baker et al.
Methylprednisolone sodium succinate	40	0.4 4	Mace et al., Baker et al.
Prednisone	30	No IDT	Venturini et al.
Prednisolone	10	No IDT	Venturini et al.
Triamcinolone acetonide	40	0.4 4 40	Baker et al., Venturini et al., Montoro et al.
Polyethylene glycol ^a	10 (1:100) 100 (1:10)	0.1 (1:10,000) 1 (1:1000) 10 (1:100)	Sohy et al.
Carboxymethylcellulose ^a	5	0.005 0.05	Venturini et al.

^a Dilutions based on literature and not personal experience, as we do not perform these tests at our institution.

acute, life-threatening nature of immediate hypersensitivity reactions, it can negatively impacts patients' quality of life [66] and have significant detrimental consequences as patients often present with worsening dermatitis failing topical corticosteroid treatment [3].

Corticosteroid dermatitis occurs more frequently in women (3:1 women to men ratio) [25]. In a review of patch testing results for 11,596 patients, of which 315 were positive, the most commonly affected occupations were housewife (18 %), office work (17 %), retired (7 %), housekeeping (6 %), education (5 %), student (5 %), and health care (4 %) [25]. The affected skin areas were hands (25 %), legs (21 %), face (20 %), feet (17 %), generalized (14 %), arms (14 %), eyes (14 %), trunk (5 %), and neck (5 %) [25].

The lesions of corticosteroid-induced contact dermatitis are nonspecific and generally present as worsening of primary dermatitis or acute eczematous dermatitis [3]. Localized edema [67, 68] or erythema-multiforme-like reactions [69–71] have been described. Patients who

received ophthalmological steroids generally present with conjunctivitis or peri-orbital edema or eczema [25]. Contact sensitization occurs most commonly via the topical route (most commonly dermatologic and less commonly ophthalmic) [25]. A proportion of patients may be sensitized via exposure to aerosolized corticosteroids, either through treatment with inhaled corticosteroids or caring for or living with patients being treated with inhaled corticosteroids [25].

Pathophysiology of Contact Dermatitis to Corticosteroids

Corticosteroids can cause contact dermatitis via a type IV cell-mediated delayed hypersensitivity reaction. As with immediate hypersensitivity reactions, contact dermatitis to topical corticosteroids can occur due to sensitization to additives or vehicles used for topical corticosteroid preparation, rather than to the actual corticosteroid itself.

Corticosteroid Structure and Cross-Reactivity

Corticosteroids have a core structure of three rings of six carbon atoms and one ring of five carbon atoms (cyclopentanoperhydrophenanthrene nucleus) [6•]. Variations in double bonds, methyl groups, acetonide bonds, and halogenation affect corticosteroid characteristics such as solubility, cutaneous preparation, and degradation [6•]. Clinical and structural studies have resulted in the Coopman classification of corticosteroids in four groups A–D [24], with further subdivision of group D by Matura and Goossens into subgroups D1 and D2 [3].

Cross-reactivity has been observed between members of the same group [3, 25, 72]. Tixocortol-21-pivalate, a group A corticosteroid, has been shown to be a good screening agent for group A corticosteroids [73, 74]. Budesonide has been found to be a good screening agent for group B corticosteroids, in which group budesonide is classified, as well as some of the group D1 corticosteroids [3].

Patch testing results are most frequently positive to group A corticosteroids, followed by group B corticosteroids, followed by group D2 corticosteroids [3, 25]. The difference in sensitization rates between corticosteroids with (D2) and without (D1) methyl and/or halogen substitution was what lead Matura and Goossens to propose the D1 and D2 subgrouping. Group D2 corticosteroids cross-react with each other and with budesonide and group A corticosteroids [3].

Pathophysiology

It has been proposed that haptenization of corticosteroids after skin penetration plays a key role in the development of sensitization. The oxidized C₂₁ position is the proposed reaction site for fixation to skin proteins [3]. This suggested mechanism is supported by observed cross-reactivity patterns [72]. Corticosteroid degradation products with an aldehyde at C₂₁ (formed via either oxidative or non-oxidative degradation) are called steroid glyoxals. The immunogenicity of several corticosteroids correlates with the ability of the steroid glyoxal breakdown products to bind arginine [75]. Given the increased frequency of positive patch testing to ethanol in corticosteroid-sensitive patients and the fact that ethanol is also degraded via aldehydes, it is possible that aldehyde formation plays a role in both ethanol and corticosteroid contact hypersensitivity [3, 76].

Diagnostic Testing

Patch testing is the standard for diagnosing contact dermatitis [77]. Tixocortol-21-pivalate (0.1 % petrolatum) and budesonide (0.01 % petrolatum) are included in the thin-layer rapid use epicutaneous test (TRUE Test) that was FDA-approved in 1995 [77]. Of the corticosteroids, tixocortol-21-pivalate and budesonide were among the top 50 allergens identified as a causative agent of contact

dermatitis over a 6-year period [78]. A combination of tixocortol-21-pivalate and budesonide identified 91.3 % of patients with corticosteroid contact dermatitis [79].

Supplemental patch testing is needed to identify the culprit corticosteroid agent in the remaining patients. A 5-year multicenter review of 427 patients evaluated with the TRUE Test found that 48 patients (12.5 %) needed supplemental patch testing (including corticosteroids) to identify the culprit allergen and 98 patients (25.6 %) were positive to additional allergens on supplemental patch testing [80]. Similarly, data from the North American Contact Dermatitis Group suggest that utilizing TRUE Test alone would fail to detect 26.7 % of culprit allergens [81]. The North American Contact Dermatitis Group includes hydrocortisone-17-butyrate (D2), clobetasol-17-propionate (D1), and triamcinolone acetonide (B), in addition to tixocortol-21-pivalate and budesonide in the core group of allergens suggested for use in allergic contact dermatitis screening [82]. In Europe, the standard corticosteroid series consists of Amcinonide (0.1 % ethanol), betamethasone-17-valerate (0.12 % ethanol), clobetasol-17-propionate (0.25 % ethanol), hydrocortisone (0.1 % ethanol), hydrocortisone-17-butyrate (1 % ethanol), triamcinolone acetonide (0.1 % ethanol), budesonide (0.1 % ethanol), prednisone (1 % ethanol), and tixocortol-21-pivalate (0.1 % petrolatum) [83].

Choosing the appropriate vehicle is essential for patch testing in order to ensure adequate skin penetration. Tixocortol-21-pivalate and budesonide prepared in petrolatum have been shown to have good sensitivity and specificity [73, 84]. Ethanol is the vehicle of choice for the other corticosteroids, with two exceptions [25]. Baeck et al. recommend diluting cortisone acetate and hydrocortisone in a 50:50 ethanol and dimethyl sulfoxide mix to improve trans-epidermal penetration [25]. When ethanol is used as the vehicle, it must be tested separately, as positive reactions to ethanol itself can occur [76]. Although corticosteroids can degrade significantly in ethanol solutions, with chromatographic purity falling 95–97 % at the end of 1 month of refrigeration at 6–8 °C [85], a subsequent study demonstrated stability up to 1 year at –18 °C [86]. Therefore, at institutions where corticosteroid patch testing is performed frequently, it may be reasonable to store solutions at –18 °C for up to 6 to 12 months [25]. Otherwise, fresh preparations should be mixed regularly [3]. Baeck et al. provide comprehensive vehicle and concentration recommendations in Table 2 of their review [25].

Topical Corticosteroid Vehicles

Vehicles used for topical corticosteroid preparation can also cause irritation or contact dermatitis. Sensitization to vehicles should be suspected in patients with negative evaluation for corticosteroids on patch testing despite a convincing history for corticosteroid-induced contact dermatitis and patients that

Table 2 Corticosteroid grouping and observed cross-reactivity patterns [3,25, 82]

Group	Corticosteroid examples in each group • Commonly used brands	Structure	Cross-reactivity
A – Hydrocortisone Type			
	Hydrocortisone • Aveeno Anti-Itch • Cortizone • Cortaid Methylprednisolone Prednisolone Tixocortol pivalate	• C ₂₁ – short-chain ester or thioester <u>Representative corticosteroid for patch test:</u> • Tixocortol-21-pivalate	1. within group 2. with group D2 corticosteroids 3. with budesonide-(S)-isomer
B – Triamcinolone Acetonide Type			
	Desonide • Desonate • Desowen Fluocinolone • Capex • Synalar Triamcinolone • Kenalog	• C ₁₆ , C ₁₇ – <i>cis</i> -ketal or –diol <u>Representative corticosteroid for patch test:</u> • Budesonide	1. within group 2. budesonide-(S)-isomer cross-reacts with group A and D2 corticosteroids
C – Betamethasone Type			
C1*	Betamethasone Dexamethasone Desoximetasone • Topicort	• C ₁₆ – methyl substitution • Halogen substitution • Non-esterified	1. betamethasone and/or dexamethasone and group B
C2*	Diffucortolone valerate Fluocortolone pivalate Clotocortolone pivalate • Cloderm	• C ₁₆ – methyl substitution • Halogen substitution • Stable esters (-valerate, -pivalate)	No significant cross-reactivity pattern observed
D – Hydrocortisone-17-Butyrate Type			
D1	Betamethasone dipropionate • Diprolene Clobetasol propionate • Clobex Mometasone fuorate • Elocon	• C ₁₆ – methyl substitution • Halogen substitution • C ₁₇ – long-chain ester • C ₂₁ – possible side chain <u>Representative corticosteroid for patch test:</u> • Clobetasol-17-propionate	1. rare cross-reactivity between aclo-methasone dipropionate and group A, budesonide, group D2
D2	Hydrocortisone-17-butyrate • Locoid • Locoid Lipocream Hydrocortisone valerate • Westcort	• C ₁₆ – no methyl substitution • No halogen substitution • C ₁₇ – long-chain ester • C ₂₁ – possible side chain Lipophilic prodrugs that penetrate skin easily <u>Representative corticosteroid for patch test:</u> • Hydrocortisone-17-butyrate	1. within group 2. with group A corticosteroids 3. with budesonide-(S)-isomer

*C1 and C2 subgrouping has been proposed by Baek et al.. However, it is not as established as the D1 and D2 subgrouping in the published literature

tolerate only specific formulations of corticosteroids. Parabens, formaldehyde-releasing preservatives (quaternium-15), isothiazolinones, lanolin, ethylenediamine, sorbitan sesquileate, fragrance, and propylene glycol are all known contact allergens commonly used in topical corticosteroid preparations [87–93]. All of these except propylene glycol

and sorbitan sesquileate are included in the TRUE Test. Propylene glycol patch testing is recommended with 30 % aqueous solutions. This concentration can have transient irritant responses but prevents false-negative results [94]. Sorbitan sesquileate patch testing can be performed with 20 % petrolatum preparations [95].

Conclusions and Recommendations for Contact Dermatitis

- Contact dermatitis is a delayed hypersensitivity reaction to corticosteroids that is reported with an incidence of 0.5 to 5 % [3].
- Suspicion should be raised for corticosteroid contact dermatitis in patients receiving topical corticosteroid treatment with worsening of primary dermatitis, an acute eczematous dermatitis, localized edema, or erythema-multiforme-like reactions.
- Patch testing is the standard for evaluation of delayed hypersensitivity. The TRUE Test includes tixocortol-21-pivalate (0.1 % petrolatum) and budesonide (0.01 % petrolatum). The combination of these two corticosteroids identifies the majority of patients with delayed hypersensitivity to corticosteroids. Supplemental corticosteroid patch testing is required to identify the remaining corticosteroid-sensitive patients.
- Cross-reactivity patterns described in Table 2 have been observed. For patients with positivity to tixocortol-21-pivalate or budesonide on TRUE testing, supplemental patch testing and consideration of cross-reactivity patterns can guide identification of a tolerated corticosteroid for therapeutic use.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Zoorob RJ, Cender D. A different look at corticosteroids. *Am Fam Physician*. 1998;58:443–50.
2. Baek M, Nicolas JF, Pilette C, Tennstedt D, Goossens A. Allergic hypersensitivity to topical and systemic corticosteroids: a review. *Allergy*. 2009;64:978–94.
3. Matura G. Contact allergy to corticosteroids. *Allergy*. 2000;55:698–704.
4. •• Patel A, Bahna S. Immediate hypersensitivity reactions to corticosteroids. *Ann Allergy Asthma Immunol*. 2015;115:178–182.e3. **Comprehensive review of IgE-mediated reactions to corticosteroids from 2004–2014.**
5. Kamm GL, Hagemeyer KO. Allergic-type reactions to corticosteroids. *Ann Pharmacother*. 1999;33:451–60.
6. •• Baker A, Empson M, The R, Fitzharris P. Skin testing for immediate hypersensitivity to corticosteroids: a case series and literature review. *Clin Exp Allergy*. 2015;45:669–76. **Case series of 23 patients evaluated for IgE-mediated reactions with skin testing.**
7. Nowak-Węgrzyn A, Shapiro G, Beyer K, Bardina L, Sampson H. Contamination of dry powder inhalers for asthma with milk proteins containing lactose. *J Allergy Clin Immunol*. 2004;113:558–60.
8. Stubbs SS, Morrell RM. Intravenous methylprednisolone sodium succinate: adverse reactions reported in association with immunosuppressive therapy. *Transplant Proc*. 1973;5:1145–6.
9. McDougal BA, Whittier FC, Cross DE. Sudden death after bolus steroid therapy for acute rejection. *Transplant Proc*. 1976;8:493–6.
10. Thompson JF, Chalmers DH, Wood RF, Kirkham SR, Morris PJ. Sudden death following high-dose intravenous methylprednisolone. *Transplantation*. 1983;36:594–6.
11. Al-Mahdy H, Hall M. Anaphylaxis and hydrocortisone. *Ann Intern Med*. 1988;108:487–8.
12. Bocanegra TS, Castañeda MO, Espinoza LR, Vasey FB, Germain BF. Sudden death after methylprednisolone pulse therapy. *Ann Intern Med*. 1981;95:122.
13. Pryse-Phillips WE, Chandra RK, Rose B. Anaphylactoid reaction to methylprednisolone pulsed therapy for multiple sclerosis. *Neurology*. 1984;34:1119–21.
14. Hayhurst M, Braude A, Benatar SR. Anaphylactic-like reaction to hydrocortisone. *S Afr Med J*. 1978;53:259–60.
15. Dajani B, Sliman N, Shubair K, Hamzeh Y. Bronchospasm caused by intravenous hydrocortisone sodium succinate (Solu-Cortef) in aspirin-sensitive asthmatics. *J Allergy Clin Immunol*. 1981;68:201–4.
16. Chan CS, Brown IG, Oliver WA, Zimmerman PV. Hydrocortisone-induced anaphylaxis. *Med J Aust*. 1984;141:444–6.
17. Mansfield LE, Ting S, Haverly RW. Anaphylaxis caused by the sodium succinate ester of hydrocortisone and methylprednisolone. *J Asthma*. 1986;23:81–3.
18. Doezeema D. Anaphylaxis following administration of intravenous methylprednisolone sodium succinate. *Am J Emerg Med*. 1987;5:42–4.
19. John GT, Thomas PP, Kirubakaran MG, Thomas M, Jacob CK, Shastry JC. Methylprednisolone sodium succinate-induced anaphylaxis in a nonatopic renal transplant recipient. *Transplantation*. 1989;48:543.
20. Sieck JO, al-Ohaly Y, Saour J, Khan M, Henriquez H. An allergic reaction to intravenous methylprednisolone administration. *Br J Clin Pract*. 1990;44:723–5.
21. Fulcher DA, Katelaris CH. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review. *Med J Aust*. 1991;154:210–4.
22. Peces R, Gorostidi M, Azofra J, Sánchez L, Alvarez J. Anaphylaxis following intravenous methylprednisolone sodium succinate in a renal transplant recipient. *Nephron*. 1991;59:497–8.
23. Husum B, Palm T, Andersen K, Vejlsted H. Immediate hemodynamic effect of pharmacological doses of methylprednisolone in dogs, and the influence of speed of injection. *Acta Anaesthesiol Scand*. 1980;24:61–4.
24. Coopman S, Degreef H, Dooms-Goossens A. Identification of cross-reaction patterns in allergic contact dermatitis from topical corticosteroids. *Br J Dermatol*. 1989;121:27–34.
25. Baek M, Chemelle J-AA, Terreux R, Drieghe J, Goossens A. Delayed hypersensitivity to corticosteroids in a series of 315 patients: clinical data and patch test results. *Contact Dermatitis*. 2009;61:163–75.
26. Venturini M, Lobera T, del Pozo MD, González I, Blasco A. Immediate hypersensitivity to corticosteroids. *J Invest Allergol Clin Immunol*. 2006;16:51–6.
27. Rodrigues-Alves R, Spínola-Santos A, Pedro E, Branco-Ferreira M, Pereira-Barbosa M. Immediate hypersensitivity to corticosteroids: finding an alternative. *J Invest Allergol Clin Immunol*. 2007;17:284–5.

28. Rachid R, Leslie D, Schneider L, Twarog F. Hypersensitivity to systemic corticosteroids: an infrequent but potentially life-threatening condition. *J Allergy Clin Immunol*. 2011;127:524–8.
29. Ehret GB, Deluze C, Dayer P, Desmeules JA. Systemic allergic reaction and diffuse bone pain after exposure to a preparation of betamethasone. *Eur J Intern Med*. 2005;16:612–4.
30. Escobosa M, Granados C, Quesada M, López A. Anaphylaxis due to methylprednisolone. *J Investig Allergol Clin Immunol*. 2008;18:407–8.
31. Aranda A, Mayorga C, Ariza A, Doña I, Blanca Lopez N, Canto G, et al. IgE mediated hypersensitivity reactions to methylprednisolone. *Allergy*. 2010;65:1376–80.
32. Calogiuri GF, Muratore GF, Nettis L, Ventura MT, Ferrannini A, Tursi A. Anaphylaxis to hydrocortisone hemisuccinate with cross sensitivity to related compounds in a paediatric patient. *Br J Dermatol*. 2004;151:707–8.
33. Angel-Pereira D, Berges-Gimeno M, Madrigal-Burgaleta R, Ureña-Tavera M, Zamora-Verduga M, Alvarez-Cuesta E. Successful rapid desensitization to methylprednisolone sodium hemisuccinate: a case report. *J Allergy Clin Immunol: In Pract*. 2014;2:346–8.
34. Kim S, Kim H. Anaphylaxis induced by oral methylprednisolone in a 10 year old boy. *Pediatr Int*. 2014;56:783–4.
35. Deruaz, Spertini, Lima S, Pasquier D, Schluep. Anaphylactic reaction to methylprednisolone in multiple sclerosis: a practical approach to alternative corticosteroids. *Mult Scler*. 2007
36. de Sousa NG, Santa-Marta C, Morais-Almeida M. Systemic corticosteroid hypersensitivity in children. *J Investig Allergol Clin Immunol*. 2010;20:529–32.
37. Nucera E, Lombardo C, Aruanno A, Colagiovanni A, Buonomo A, de Pasquale T, et al. “Empty sella syndrome”: a case of a patient with sodium succinate hydrocortisone allergy. *Eur J Endocrinol*. 2011;164:139–40.
38. Calogiuri GF, Nettis E, Di Leo E, Muratore L, Ferrannini A, Vacca A. Long-term selective IgE-mediated hypersensitivity to hydrocortisone sodium succinate. *Allergol Immunopathol (Madr)*. 2013;41:206–8.
39. Compalati E, Guerra L, Rogkakou A, Zanella C, Scordamaglia A, Passalacqua G. Angioedema after administration of methylprednisolone to treat drug allergy. *Allergy*. 2007;62:1346–8.
40. Currie G, Paterson E, Keenan F, Nath S, Watt S. An unexpected response to intravenous hydrocortisone succinate in an asthmatic patient. *Br J Clin Pharmacol*. 2005;60:342.
41. Caimmi S, Caimmi D, Bousquet PJ, Demoly P. Succinate as opposed to glucocorticoid itself allergy. *Allergy*. 2008;63:1641–3.
42. Gelincik A, Yazici H, Emre T, Yakar F, Buyukozturk S. An alternative approach to a renal transplant patient who experienced an immediate type systemic reaction due to methylprednisolone sodium succinate. *J Investig Allergol Clin Immunol*. 2009;19:162–3.
43. Koutsostathis N, Vovolis V. Severe immunoglobulin E-mediated anaphylaxis to intravenous methylprednisolone succinate in a patient who tolerated oral methylprednisolone. *J Investig Allergol Clin Immunol*. 2009;19:330–2.
44. Walker AI, Råwer H-C, Sieber W, Przybilla B. Immediate-type hypersensitivity to succinylated corticosteroids. *Int Arch Allergy Immunol*. 2010;155:86–92.
45. Eda A, Sugai K, Shioya H, Fujitsuka A, Ito S, Iwata T, et al. Acute allergic reaction due to milk proteins contaminating lactose added to corticosteroid for injection. *Allergol Int*. 2009;58:137–9.
46. Savvatanos S, Giavi S, Stefanaki E, Siragakis G, Manousakis E, Papadopoulos NG. Cow’s milk allergy as a cause of anaphylaxis to systemic corticosteroids. *Allergy*. 2011;66:983–5.
47. Levy Y, Segal N, Nahum A, Marcus N, Garty B-Z. Hypersensitivity to methylprednisolone sodium succinate in children with milk allergy. *J Allergy Clin Immunol In Pract*. 2014;2:471–4.
48. Laing ME, Fallis B, Murphy GM. Anaphylactic reaction to intraslesional corticosteroid injection. *Contact Dermatitis*. 2007;57:132–3.
49. Field S, Falvey E, Barry J, Bourke J. Type 1 hypersensitivity reaction to carboxymethylcellulose following intra articular triamcinolone injection. *Contact Dermatitis*. 2009;61:302–3.
50. Steiner U, Gentinetta T, Hausmann O, Pichler W. IgE-mediated anaphylaxis to intraarticular glucocorticoid preparations. *AJR Am J Roentgenol*. 2009;193:W156–7.
51. Hadithy A, van Maaren M, Vermes A. Anaphylactic reactions following Kenacort A® injection: carboxymethylcellulose is involved once again. *Contact Dermatitis*. 2011;64:179–80.
52. Patterson DL, Yunginger JW, Dunn WF, Jones RT, Hunt LW. Anaphylaxis induced by the carboxymethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). *Ann Allergy Asthma Immunol*. 1995;74:163–6.
53. Dewachter P, Mouton-Faivre C. Anaphylaxis to macrogol 4000 after a parenteral corticoid injection. *Allergy*. 2005;60:705–6.
54. Sohy C, Vandenplas O, Sibille Y. Usefulness of oral macrogol challenge in anaphylaxis after intra articular injection of corticosteroid preparation. *Allergy*. 2008;63:478–9.
55. Moran D, Moynagh M, Alzanki M, Chan V, Eustace S. Anaphylaxis at image-guided epidural pain block secondary to corticosteroid compound. *Skelet Radiol*. 2012;41:1317–8.
56. Borderé A, Stockman A, Boone B, Franki A, Coppens M, Lapeere H, et al. A case of anaphylaxis caused by macrogol 3350 after injection of a corticosteroid. *Contact Dermatitis*. 2012;67:376–8.
57. Spoerl D, Scherer K, Bircher A. Contact urticaria with systemic symptoms due to hexylene glycol in a topical corticosteroid: case report and review of hypersensitivity to glycols. *Dermatology*. 2010;220:238–42.
58. Drug allergy: an updated practice parameter. *Ann. Allergy Asthma Immunol*. 2010;105:259–273.
59. Muroi N, Nishibori M, Fujii T, Yamagata M, Hosoi S, Nakaya N, et al. Anaphylaxis from the carboxymethylcellulose component of barium sulfate suspension. *N Engl J Med*. 1997;337:1275–7.
60. Bigliardi PL, Izakovic J, Weber JM, Bircher A. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. *Dermatology*. 2003;207:100–3.
61. Asakawa H, Araki T, Imai I, Tsutsumi Y, Kawakami F. Skin tests of steroid allergy. *Allergy*. 1999;54:645–6.
62. Figueredo E, Cuesta-Herranz JI, De Las Heras M, Lluch-Bernal M, Umpierrez A, Sastre J. Anaphylaxis to dexamethasone. *Allergy*. 1997;52:877.
63. Mace S, Vadas P, Pruzanski W. Anaphylactic shock induced by intraarticular injection of methylprednisolone acetate. *J Rheumatol*. 1997;24:1191–4.
64. Montoro J, Valero A, Serra Baldrich E, Amat P, Lluch M, Malet A. Anaphylaxis to paramethasone with tolerance to other corticosteroids. *Allergy*. 2000;55:197–8.
65. Vatti R, Ali F, Teuber S, Chang C, Gershwin E. Hypersensitivity reactions to corticosteroids. *Clin Rev Allergy Immunol*. 2013;47:26–37. **Comprehensive review of immediate and delayed corticosteroid-induced reactions.**
66. Skoet R, Zachariae R, Agner T. Contact dermatitis and quality of life: a structured review of the literature. *Br J Dermatol*. 2003;149:452–6.
67. Rodríguez-Serna M, Silvestre JF, Quecedo E, Martínez A, Miguel FJ, Gauchía R. Corticosteroid allergy: report of 3 unusually acute cases. *Contact Dermatitis*. 1996;35:361–2.
68. Miranda Romero A, Sánchez Sambucety P, Bajo C, Martinez M, Garcia Munoz M. Genital oedema from contact allergy to prednicarbate. *Contact Dermatitis*. 1998;38:228.
69. Valsecchi R, Reseghetti A, Leghissa P, Cologni L, Cortinovis R. Erythema-multiforme-like lesions from triamcinolone acetonide. *Contact Dermatitis*. 1998;38:362–3.

70. Stingeni L, Caraffini S, Assalve D, Lapomarda V, Lisi P. Erythema-multiforme-like contact dermatitis from budesonide. *Contact Dermatitis*. 1996;34:154–5.
71. Calista D, Schianchi S. Erythema multiforme-like eruption induced by contact dermatitis caused by topical corticosteroids. *G Ital Dermatol Venereol*. 2008;143:227–8.
72. Lepoittevin JP, Drieghe J, Dooms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. *Arch Dermatol*. 1995;131:31–7.
73. Wilkinson SM, English JS. Hydrocortisone sensitivity: a prospective study of the value of tixocortol pivalate and hydrocortisone acetate as patch test markers. *Contact Dermatitis*. 1991;25:132–3.
74. Lauerma AI, Tarvainen K, Forström L, Reitamo S. Contact hypersensitivity to hydrocortisone-free-alcohol in patients with allergic patch test reactions to tixocortol pivalate. *Contact Dermatitis*. 1993;28:10–4.
75. Wilkinson SM, Jones MF. Corticosteroid usage and binding to arginine: determinants of corticosteroid hypersensitivity. *Br J Dermatol*. 1996;135:225–30.
76. Matura M, Lepoittevin JP, Arbez Gindre C, Goossens A. Testing with corticosteroid aldehydes in corticosteroid sensitive patients (preliminary results). *Contact Dermatitis*. 1998;38:106–8.
77. Fonacier L, Sher J. Allergic contact dermatitis. *Ann Allergy Asthma Immunol*. 2014;113:9–12.
78. Saripalli Y, Achen F, Belsito D. The detection of clinically relevant contact allergens using a standard screening tray of twenty-three allergens. *J Am Acad Dermatol*. 2003;49:65–9.
79. Boffa MJ, Wilkinson SM, Beck MH. Screening for corticosteroid contact hypersensitivity. *Contact Dermatitis*. 1995;33:149–51.
80. Camacho-Halili M, Axelrod S, Michelis M, Lighvani S, Khan F, Leon S, et al. A multi-center, retrospective review of patch testing for contact dermatitis in allergy practices. *Ann Allergy Asthma Immunol*. 2011;107:487–92.
81. Warshaw EM, Belsito DV, Taylor JS, Sasseville D, DeKoven JG, Zirwas MJ, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. *Dermatitis*. 2013;24:50–9.
82. Schalock P, Dunnick C, Nedorost S, Brod B, Warshaw E, Mowad C. American Contact Dermatitis Society Core Allergen Series. *Dermatitis*. 2013;24:7.
83. Ljubojevic S, Lipozencic J, Basta-Juzbasic A. Contact allergy to corticosteroids and *Malassezia furfur* in seborrhoeic dermatitis patients. *J Europ Acad Dermatol Venereol Jeadv*. 2010;25:647–51.
84. Wilkinson SM, Beck MH. Corticosteroid contact hypersensitivity: what vehicle and concentration? *Contact Dermatitis*. 1996;34:305–8.
85. Förström L, Lassus A, Salde L, Niemi KM. Allergic contact eczema from topical corticosteroids. *Contact Dermatitis*. 1982;8:128–33.
86. Isaksson M, Gruvberger B, Persson L, Bruze M. Stability of corticosteroid patch test preparations. *Contact Dermatitis*. 2000;42:144–8.
87. Yim E, Baquerizo Nole KL, Tosti A. Contact dermatitis caused by preservatives. *Dermatitis*. 2014;25:215–31.
88. Wolf R, Orion E, Ruocco E, Baroni A, Ruocco V. Contact dermatitis: facts and controversies. *Clin Dermatol*. 2013;31:467–78.
89. Hogan DJ. Allergic contact dermatitis to ethylenediamine. A continuing problem. *Dermatol Clin*. 1990;8:133–6.
90. Asarch A, Scheinman PL. Sorbitan sesquioleate, a common emulsifier in topical corticosteroids, is an important contact allergen. *Dermatitis*. 2008;19:323–7.
91. Funk JO, Maibach HI. Propylene glycol dermatitis: re-evaluation of an old problem. *Contact Dermatitis*. 1994;31:236–41.
92. Warshaw EM, Botto NC, Maibach HI, Fowler JF, Rietschel RL, Zug KA, et al. Positive patch-test reactions to propylene glycol: a retrospective cross-sectional analysis from the North American Contact Dermatitis Group, 1996 to 2006. *Dermatitis*. 2009;20:14–20.
93. Coloe J, Zirwas MJ. Allergens in corticosteroid vehicles. *Dermatitis*. 2008;19:38–42.
94. Nelson J, Mowad C. Allergic Contact Dermatitis: patch testing beyond the TRUE Test. *J Clin Aesthet Dermatol*. 2010;3:36–41.
95. Pereira F, Cunha H, Dias M. Contact dermatitis due to emulsifiers. *Contact Dermatitis*. 1997;36:114.