

The Impact of Corticosteroid Allergy

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Opinion statement

The key to treatment of corticosteroid allergy, especially delayed-type reactions to topical corticosteroids, is in recognizing it as a possible diagnosis. Corticosteroids are among the most important anti-inflammatory agents in a physician's therapeutic armamentarium; these medications are the cornerstone of treatment for most dermatoses and may be overlooked as the culprit in cases of refractory dermatitis. Clues to possible corticosteroid allergy include persistence or worsening of dermatitis with the use of an appropriate agent or a change in the clinical pattern of disease. Patients may neglect to mention use of over-the-counter topical corticosteroid use; the possibility of corticosteroid contact allergy is more likely in those with chronic dermatoses such as atopic or stasis dermatitis. Once suspected, corticosteroid allergy can be confirmed by a repeat open application test (ROAT) with the suspect medicament agent in addition to standard patch testing. Patch testing techniques that may improve diagnostic accuracy include testing to agents from all classes, performing a late (7–10-day) reading, and considering “rim reactions” as likely relevant. Once the patient's allergy is known, the clinician can choose a safe alternative. To minimize the risk of inducing corticosteroid allergy, physicians should consider prescribing agents that are less allergenic, e.g., those in classes C or D1, especially for patients with chronic skin disease.

Introduction

Corticosteroid allergy is a counter-intuitive phenomenon and, because of this, likely under recognized. While these medications are meant to quell inflammation, some can act as haptens and drive an allergic response. Further, their anti-inflammatory properties can mask a

reaction confounding the clinical picture and leading to delayed or misdiagnosis.

For a given molecule, the risk of inducing a contact allergy is influenced by both the potency of the allergen and the nature of the exposure, including the dose and

the frequency, whether applied under occlusion, etc. [1]. While corticosteroids of many forms have the potential to induce allergy, this most commonly manifests as contact allergy to topically applied steroid medications, with a reported frequency of 0.5–5 % [2••]. However, immediate-type reactions do occur and should not be ignored given their severity.

Corticosteroid allergy should be suspected in patients who paradoxically worsen despite seemingly appropriate treatment. Several diagnostic modalities, including skin prick testing, repeat open application

testing (ROAT), epicutaneous standard patch testing, and intradermal skin testing, are available in the clinician's armamentarium. If a patient tests positive on ROAT or patch testing, one should consider extended corticosteroid patch testing series in patients who are likely to require chronic corticosteroids. Doing so will aid the clinician in selecting the appropriate topical agent for therapy.

This review will focus on the various types of corticosteroid allergy, the scope of their impact and the implications for both patients and providers.

Immediate hypersensitivity reactions

Immediate hypersensitivity reactions to corticosteroids are decidedly rare but can have devastating consequences if unrecognized. Patel et al. reviewed all reported cases of corticosteroid allergy between 2004 and 2014 and found an overall prevalence of 0.1–0.3 % for immediate-type reactions [3•]. These occurred in a variety of age groups (ages 2–90) and roughly equally in men and women. The most common clinical manifestation was anaphylaxis, followed by urticaria or angioedema, though bronchospasm and rash were also reported [4, 5, 6].

Most cases followed intravenous exposure of methylprednisolone and hydrocortisone, though incidence following oral exposures and intra-articular exposures was also seen [7]. Increased risk of immediate corticosteroid allergy was seen in patients with a history of renal transplantation, asthma, or non-steroidal anti-inflammatory drug (NSAID) allergy, though this may be a reflection of increased corticosteroid exposure in these patients [8]. While many agents have been implicated in case reports, oral prednisone and dexamethasone seem to be associated with a lower incidence of anaphylaxis and should be used whenever possible [8].

Finally, in a significant minority of cases (28 %), an inactive ingredient was found to be the culprit allergen, rather than the corticosteroid molecule itself [3•]. Succinate ester and lactose were the most common offenders. Inactive ingredients were responsible for 37 % of all cases of anaphylaxis and must not be overlooked when evaluating a patient with suspected corticosteroid hypersensitivity.

While immediate hypersensitivity reactions must be suspected and managed expediently, further diagnostic workup includes referral to an allergy and immunology specialist for skin prick testing or intradermal testing. Skin prick testing is performed using an undiluted suspected agent [3•]. If negative, intradermal testing is generally done with injection of varying concentrations of the suspected culprit medication. Both 1:100 and 1:1000 dilutions have been reported [9, 10]. Skin prick or intradermal testing can be performed for additives and inactive ingredients in preparations as well. Additionally, if initial testing is negative, a graded dose challenge test is considered if the culprit remains uncertain and anaphylaxis is an unlikely event. It is typical to start at 1/10 the usual dose and observe for 1–1.5 h. If no reaction is seen, then a full

dose is given. This should always be done in a clinical setting that is equipped to treat anaphylaxis and by clinicians trained in administering these tests [11].

This same testing can also be used to identify an appropriate alternative agent for treatment. However, very rarely, an alternative agent cannot be identified with the above testing and desensitization may be required. This consists of starting at a very low dose or concentration of medication, suggested by Macy to be 1/1000 the final dose. The dose is then increased every 15 min, ultimately reaching the full dose over several hours [11].

Delayed hypersensitivity reactions

Delayed hypersensitivity reactions, most commonly manifesting as allergic contact dermatitis (ACD), have an overall prevalence of 0.2–5 %, though estimates vary by study [12]. Importantly, the prevalence is influenced by regional variation in over-the-counter product availability, as well as variation in prescribing habits. Further, the availability of agents in the pharmaceutical market, as well as the test and detection methods of a given locale, also impacts these estimates [13]. For example, Wattanakrai et al. found an increased positive-reaction rate for D1 esters (clobetasol-17-propionate, betamethasone dipropionate, etc.) in Thailand, while these reactions are very rare in Europe and the USA. They hypothesized that this was due to the fact that these agents are available without a prescription in Thailand, whereas only hydrocortisone is available over the counter in most countries [14]. These factors have substantial implications for patients and providers as discussed below.

Clinically, delayed hypersensitivity reactions to corticosteroids most commonly manifest as a worsening of the primary dermatologic symptoms after topical treatment. Reactions including acute eczema, local edema, and an id-like spread elsewhere on the body have all been reported [2••]. Eruptions more commonly occur on the hands, legs, and face. However, delayed reactions following intra-ocular, inhalational, and intramuscular treatments have also been reported [15, 16]. Bennett et al. noted that 13 % of patients using inhaled or intranasal corticosteroids for treatment of allergic rhinitis or asthma manifested positive patch test reactions to corticosteroids themselves or preservatives within their vehicles [17]. Delayed reactions have also been reported following intra-articular injection of methylprednisolone and triamcinolone acetonide [18]. Finally, a minority of patients will manifest a delayed generalized eruption following systemic administration of a corticosteroid that had previously been applied topically [19]. Fowler described a patient with an allergy to hydrocortisone that developed systemic contact dermatitis after being given a cross-reacting corticosteroid, prednisolone [20].

Theoretically, any patient exposed to corticosteroids is at risk for developing an allergy. However, studies have repeatedly shown an increased risk of corticosteroid allergy in a subset of patients. Overall, women are nearly three times more likely to present with a corticosteroid allergy than their male counterparts, perhaps due to self-treatment and usage patterns more likely than hormonal factors. Further, a personal history of atopy or other inflammatory skin disease increases one's risk of developing corticosteroid allergy, with atopic dermatitis, chronic facial dermatitis, and stasis dermatitis being the most common [15, 16]. In a series of 315 patients with positive patch testing to corticosteroids, 34 %

had a personal history of atopy. While it was previously thought that patients with atopic dermatitis were less likely to manifest contact dermatitis due to impaired cellular immunity, studies have, in fact, suggested the opposite. Kot et al. showed that these patients not only are more likely to manifest contact allergy to topical steroids (12.8 % of patients), but also have a significantly increased risk of allergic contact dermatitis to allergens in general (nearly half of all patients) [21]. Patients with chronic leg ulcers are also at increased risk. Barbaud et al. found that 8 % of patients in this population tested positive for corticosteroid allergy, and the prevalence was even higher among patients with a surrounding eczematous dermatitis [22]. This increased risk likely reflects both an increased use of corticosteroids in these populations, as well as a predisposition toward allergy secondary to an impaired skin barrier.

Finally, as with immediate hypersensitivity reactions, it is important to consider the possibility that the culprit antigen may be a vehicle component, rather than the corticosteroid molecule itself. Coloe and Zirwas surveyed every corticosteroid in widespread use in the USA and found that more than two thirds of the vehicles contained at least one well-known allergen, with propylene glycol being the most common [23]. Other common excipients, in decreasing order of frequency of patch test reactions, were imidazolidinylurea, diazolidinylurea, methylchloroisothiazolinone/methylisothiazolinone, lanolin, sorbitan sesquioleate, and parabens. Improved understanding of these concepts can guide clinicians in selecting medications with the least allergenic potential.

Corticosteroid molecules and cross-reactivity

With regard to their potential antigenicity, not all corticosteroid molecules are created equally. In fact, much of the work in this field has focused on classifying chemically similar agents with the potential for cross-reactivity in an effort to guide the diagnosis and management of steroid-allergic patients. The original classification was proposed in 1989 by Coopman et al. which stratified molecules into four groups (A, B, C, D) based on an analogous substitution pattern on the steroid D ring or the carbon side chain (C_{20} , C_{21}) [24••]:

- Group A: hydrocortisone type: no substitution on the D ring except a short-chain ester on C_{21} or a thioester on C_{21}
- Group B: triamcinolone acetonide type: C_{16} , C_{17} -cis-ketal or -diol structure
- Group C: betamethasone type: C_{16} -methyl substitution
- Group D: hydrocortisone-17-butyrate type: long-chain ester at C_{17} or C_{17} and C_{21} with or without C_{16} -methyl substitution

In 2000, Matura et al. proposed a subdivision of group D into two groups based on their metabolism in the skin (Table 1):

- Group D1: containing C_{16} -methyl substitution and halogenation on the B ring
 - Group D2: labile ester steroids that lack both substitutions
- Importantly, these classification schemes group corticosteroids based upon cross-reactivity patterns rather than their sensitizing potential as

Table 1. Classification of corticosteroids, modified from Coopman and Matura

Group	Characteristics of the group	Typical members	Possible cross-reactions
A	No substitution on the D ring except a short-chain ester or a thioester on C ₂₁	Cortisone acetate Fludrocortisone acetate Fluorometholone Hydrocortisone Hydrocortisone acetate Hydrocortisone 21-butyrate Methylprednisolone acetate Prednisolone Prednisolone pivalate Prednisone Tixocortol pivalate	D2
B	C ₁₆ , C ₁₇ cis-ketal or diol structure. Possibly a side chain on C ₂₁	Amcinonide Budesonide Desonide Fluocinolone acetonide Fluocinonide Halcinonide Triamcinolone Triamcinolone acetonide	
C	C ₁₆ methyl substitution on the D ring. Halogen substitution. No side chain on C ₁₇ . Possibly a side chain on C ₂₁	Betamethasone Betamethasone sodium phosphate Desoximetasone Dexamethasone Dexamethasone acetate Diflucortolone valerate Flumethasone pivalate Fluocortolone Halometasone	
D1	Methyl substitution on C ₁₆ . Halogen substitution. Side chain ester on C ₁₇ . Possibly a side chain on C ₂₁	Alclomethasone dipropionate Beclomethasone dipropionate Betamethasone dipropionate Betamethasone 17-valerate Clobetasol propionate Clobetasone butyrate Diflorasone diacetate Fluticasone propionate Mometasone furoate	
D2	No methyl substitution on C ₁₆ . No halogen substitution. Side chain ester on C ₁₇ . Possibly a side chain on C ₂₁	Hydrocortisone aceponate Hydrocortisone 17-butyrate Methylprednisolone aceponate Prednicarbate	A Budesonide (S isomer)

Coopman et al. [24••], Matura [2•]

an allergen. For example, positive reactions are frequently observed in group A, group B, and group D2, whereas agents in group C and group D1 rarely produce positive results [3].

Finally, more recently, Baeck et al. proposed a three-part classification system (Table 2) based upon the observation that positive patch test reactions were seen much more frequently to molecules with no C16-methyl substitution or halogenation (groups A and D2 above):

- Group 1: the nonmethylated, most often nonhalogenated molecules (mostly groups A and D2 above)
- Group 2: the halogenated molecules with a C₁₆/C₁₇-cis-ketal or -diol structure (group B above)
- Group 3: the halogenated and C₁₆-methylated molecules (mostly groups C and D1 above)

In addition to proposing a simplified classification system, they also proposed two subsets of corticosteroid-allergic patients. The first type was patients who reacted only to molecules classified within a specific cluster. However, the second type was patients who reacted to molecules from at least two different clusters, suggesting that a subset of patients exist who may react to the entire spectrum of corticosteroids, as discussed further below [25••].

When examining patch test data, the highest rate of positive reactions was seen with molecules from group A, followed by those from group D2. In one study of corticosteroid-allergic patients, 61 % reacted to budesonide (group B), 43 % to tixocortol pivalate (group A), and 31 % to hydrocortisone-17-butyrate (group D2). Importantly, the majority of patients with corticosteroid allergy reacted positively to more than one molecule in the corticosteroid series, which underscores the importance of expanded testing in this patient population as discussed below [26].

Diagnostic approach

The entire diagnostic approach depends upon the initial suspicion that a patient has an allergy to corticosteroids. For patients with persistent dermatitis despite the use of appropriate topical corticosteroids, patch testing may have the most utility as an initial screening tool [27]. Whether or not a specific corticosteroid allergen is suspected, patch testing can prove invaluable as many patients manifest reactions to more than one agent. In Baeck's study, more than 80 % of patients with tixocortol pivalate allergy, and more than 90 % of those with budesonide allergy, reacted positively to other corticosteroid molecules [26]. These two markers are reportedly able to detect 88–91 % of corticosteroid-allergic patients [26, 28]. Inclusion of hydrocortisone 17-butyrate enabled the detection of an additional 4 % of patients. Importantly, when positive reactions to corticosteroids are identified, they are highly clinically relevant [29]. Formulations of both the FDA-approved T.R.U.E TestTM (SmartPractice, Arizona) and non-FDA-approved North

Table 2. Baeck's 3-part classification scheme of corticosteroid cross-reactivity, modified

Groups	Characteristics	Typical members
1(A, D2), budesonide	No C16-methyl substitution No halogen substitution in most cases	Budesonide Cortisone acetate Fludrocortisone acetate Fluorometholone Fluprednisolone acetate Hydrocortisone Hydrocortisone aceponate Hydrocortisone acetate Hydrocortisone 17-butyrate Hydrocortisone 21-butyrate Methylprednisolone aceponate Methylprednisolone acetate Prednicarbate Prednisolone Prednisolone pivalate Prednisolone succinate Prednisone Tixocortol pivalate Triamcinolone
2 (B)	C ₁₆ /C ₁₇ cis-ketal or diol structure Halogen substitution except*	Amcinonide Desonide* Fluocinolone acetonide Fluocinonide Halcinonide* Triamcinolone acetonide Triamcinolone diacetate
3 (C, D1)	C ₁₆ -methyl substitution Halogen substitution	Alclomethasone dipropionate Beclomethasone dipropionate Betamethasone Betamethasone 17-valerate Betamethasone dipropionate Clobetasol propionate Clobetasone butyrate Desoximetasone Dexamethasone Dexamethasone acetate Dexamethasone sodium phosphate Diflorasone diacetate Fluocortolone Fluocortolone pivalate Fluticasone propionate Mometasone furoate

Baeck et al. [25••]

American Baseline Series (Chemotechnique-Dormer Laboratories, Toronto and Allergeaze, Smartpractice, Arizona) contain these three allergens. However, in some cases, true allergens may be missed with initial screening, and expanded testing may be useful [26]. There are several commercially available extended patch test series for topical corticosteroids, which can provide further beneficial information for patients who test positive using either of the above screening series. These non-FDA-approved specialty series are available from both Chemotechnique-Dormer and SmartPractice.

The canonical methodology applied to performing patch testing for any suspected contact allergen holds true with suspected steroid allergy as well. Ideally, patients should be free of any active dermatitis prior to placing the patches, though this may not always be feasible. Patches should be applied and then removed after 48 h [27]. A consensus from the European Society for Contact Dermatitis recommends that at least two readings of the patch test reactions are required. Ideally, readings are performed on days 2, 3, or 4 and around day 7. Many clinicians perform an extended reading on day 7 though data from some authors suggests few patients will develop a positive after day 5 [30]. Rim erythema or “edge effects” are noticed in some patients and often represent a precursor to a later eczematous reaction. These patterns could represent a partial or early reaction to the compound or indicate that differing levels of steroid concentrations within the patch itself may have a protective effect against the full manifestation of the allergy [31].

Importantly, however, some authors have questioned the reproducibility and validity of epicutaneous patch testing, citing variable percutaneous absorption and inherent anti-inflammatory nature of corticosteroids leading to false-negative results, and instead suggested intradermal or skin prick testing [32]. To this end, Mimesh et al. examined both the reproducibility of epicutaneous patch testing and the concordance between patch and intradermal testing. They found the reproducibility of patch testing with corticosteroid molecules to range from 66 to 100 % and a concordance rate of 89 % between the two diagnostic modalities. They proposed that intradermal testing might be most useful if patch test results are negative despite a strong clinical suspicion of corticosteroid allergy [33].

In addition to intradermal or skin prick testing, if there is a suspected culprit not confirmed by patch testing, there are two additional options. Some studies have suggested that repeat patch testing may be beneficial. Soni et al. showed that some patients who fail to react on initial testing develop clinically relevant, positive reactions upon repeat testing [34]. However, others suggest that repeat patch testing can lead to an autosensitization reaction [35]. Finally, the clinician can also consider repeat open application test (ROAT). ROAT is generally performed by applying the suspected allergen to an area of normal, unaffected skin of the volar forearm twice daily for up to 14 days or until a reaction develops. In early studies using various compounds to test the reliability of patch testing as compared to ROAT,

approximately 44 % of patients who had equivocal or negative results to patch testing had a positive ROAT [36].

Treatment and management strategies

Management of delayed-type hypersensitivity reactions to corticosteroids rests upon removing the offending agent and finding effective alternative therapy when needed (Fig. 1). As mentioned earlier, agents classified in groups C and D1 (Table 1) or group 3 (Table 2) are the least likely to produce contact allergy. Further, regarding vehicle allergy, generic versions are less likely to contain allergenic vehicles than branded versions, and solution and ointment formulations are the least allergenic vehicles [23]. However, given the possibility that a patient may manifest multiple allergies, expanded testing to identify tolerable agents is preferred over trial-and-error via switching groups, particularly in patients who will need long-term treatment.

Further, as proposed by Baeck et al., there may exist a subset of patients who react to the corticosteroid carbon backbone, which is relatively conserved among all agents [25••]. For example, one case report described a patient who manifested cross-reactivity among agents in groups B, C, and D, including agents in group D1, which is traditionally thought to be less

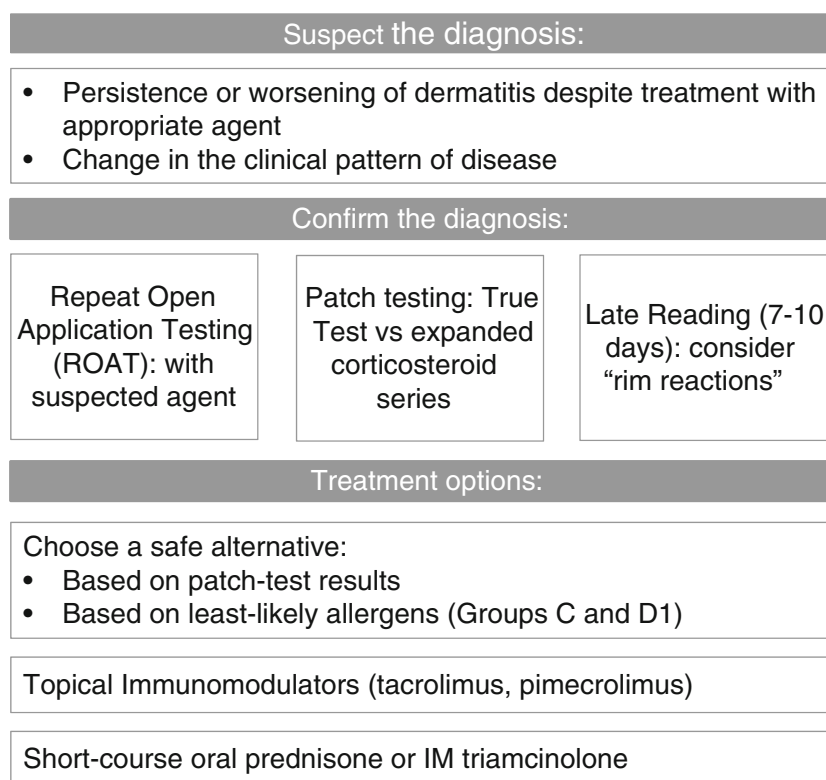


Fig. 1. The diagnosis and management of corticosteroid allergy. The critical first step involves suspecting allergy in the first place. Several options exist for confirmatory testing and management rests upon finding an alternative treatment option.

allergenic [37]. In these cases, clinicians must consider alternative treatments as discussed below.

Topical immunomodulators, such as tacrolimus and pimecrolimus, represent alternative agents to consider in the corticosteroid-allergic patient. These agents can provide either short-term relief until an alternative topical corticosteroid can be found, or may be used as a primary agent to avoid the use of topical corticosteroids altogether. Many studies have shown comparable efficacy between topical corticosteroids and topical immunomodulators in various dermatoses, including atopic dermatitis and vitiligo [38, 39]. Additionally, for patients with chronic and severe underlying dermatoses, steroid-sparing modalities such as phototherapy, cyclosporine, and methotrexate represent additional therapeutic options.

However, in the case of an exuberant or systemic contact dermatitis, these agents may provide insufficient immediate relief. Anecdotally, it is our experience that patients with exuberant allergic contact dermatitis to topical steroids often can be safely and effectively treated with a short course of oral prednisone or intramuscular triamcinolone. Of course, the clinician should monitor for paradoxical worsening which may indicate cross-reactivity. In one study of corticosteroid-allergic patients, 5 % developed delayed hypersensitivity following oral administration of a steroid, most commonly methylprednisolone, which had previously been applied topically [19]. However, many studies note that traditional patterns of cross-reactivity are inconsistent when applied to systemic corticosteroids, citing patients who tolerated prednisone and prednisolone despite allergy to methylprednisolone and hydrocortisone [40, 41]. Thus, clinical correlation and close monitoring is key.

It is also important to note that if a patient is required to abruptly discontinue all topical steroids, there is the potential for steroid withdrawal. Hajar et al. [42] found that steroid withdrawal occurred most frequently with chronic or overuse of mid to high potency corticosteroids, predominantly in women using them daily on their face or genitals for atopic dermatitis or cosmetic reasons. The most common symptoms of withdrawal are burning/stinging, photosensitivity, pruritus, pain, and hot flashes. There are two major clinical variants of withdrawal, either the papulopustular or erythroedematous variety. Hajar et al. found that the papulopustular variant was treated more often with antibiotics while antihistamines, cool compresses, and psychological support were used most often in the erythroedematous variety.

Conclusions

Allergy to corticosteroids is a real phenomenon and often underappreciated due to its paradoxical nature. However, for patients with chronic conditions requiring continual topical or oral steroid use, the consequences of refractory dermatitis, or rarely life-threatening reactions, make identification of this entity critical to their care. Clinicians' increased awareness of these

allergies will make early diagnosis more likely and lead to more effective management strategies.

Compliance with Ethical Standards

Conflict of Interest

Dr. Sara Harcharik Perkins declare that they have no conflict of interest.

Dr. Christopher R Stamey declare that they have no conflict of interest.

Dr. Kalman L. Watsky edits a section on Prurigo Nodularis for UpToDate.

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.

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