

Hypersensitivity Reactions to Corticosteroids

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Abstract Hypersensitivity reactions to corticosteroids (CS) are rare in the general population, but they are not uncommon in high-risk groups such as patients who receive repeated doses of CS. Hypersensitivity reactions to steroids are broadly divided into two categories: immediate reactions, typically occurring within 1 h of drug administration, and non-immediate reactions, which manifest more than an hour after drug administration. The latter group is more common. We reviewed the literature using the search terms “hypersensitivity to steroids, adverse effects of steroids, steroid allergy, allergic contact dermatitis, corticosteroid side effects, and type I hypersensitivity” to identify studies or clinical reports of steroid hypersensitivity. We discuss the prevalence, mechanism, presentation, evaluation, and therapeutic options in corticosteroid hypersensitivity reactions. There is a paucity of literature on corticosteroid allergy, with most reports being case reports. Most reports involve non-systemic application of corticosteroids. Steroid hypersensitivity has been associated with type I IgE-mediated allergy including anaphylaxis. The overall prevalence of type I steroid hypersensitivity is estimated to be 0.3–0.5 %. Allergic contact dermatitis (ACD) is the most commonly reported non-immediate hypersensitivity reaction and usually follows topical CS application. Atopic dermatitis and stasis dermatitis of the lower extremities are risk factors for the development of ACD from topical CS. Patients can also develop hypersensitivity reactions to nasal, inhaled, oral,

and parenteral CS. A close and detailed evaluation is required for the clinician to confirm the presence of a true hypersensitivity reaction to the suspected drug and choose the safest alternative. Choosing an alternative CS is not only paramount to the patient’s safety but also ameliorates the worry of developing an allergic, and potentially fatal, steroid hypersensitivity reaction. This evaluation becomes especially important in high-risk groups where steroids are a life-saving treatment. The assessment should be done when the patient’s underlying condition is in a quiescent state.

Keywords Corticosteroids · Glucocorticoids · Steroids · Hypersensitivity · Sensitization · Allergy · Cross-reactivity · Anaphylaxis · Asthma · Atopy · Topical · Systemic · Allergic contact dermatitis · Delayed type · Immediate type · Non-immediate reactions · Inhaled steroid · Intranasal steroid · Intra-articular steroid · Systemic steroid · Allergic reaction · The Coopman steroid classification system

Introduction

The clinical effects of corticosteroids (CS) were discovered in the 1940s and spawned a billion dollar industry that provided clinical benefits to patients with a multitude of conditions. Corticosteroids are commonly employed in the treatment of asthma, allergic disorders, autoimmune conditions, post-transplantation regimens, drug-induced lupus, and other immunologically mediated disorders due to their anti-inflammatory and immunosuppressive properties [1–4]. They are also used in many disorders that are not immediately perceived as inflammatory or immunologic, such as orthopedics, cardiology, dermatology, nephrology, and oncology. Years after the discovery of the beneficial effects of corticosteroids, it was gradually apparent that these positive effects came at a price, and we now appreciate the significant adverse effects of steroids, ranging from hypertension, cataracts, diabetes, hypothalamus–pituitary–adrenal (HPA)

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axis suppression, growth retardation, immunosuppression, osteonecrosis, and osteoporosis. Allergic or hypersensitivity reactions to steroids are not considered a common serious adverse effect, and there is scant information regarding these conditions reported in the literature.

Because of this, and in spite of their widespread use, physicians seldom suspect them of causing a hypersensitivity reaction. Indeed, such a concept would seem counter-intuitive or paradoxical given their well-documented anti-inflammatory properties. In addition, it can be challenging for the clinician to distinguish between a hypersensitivity reaction and deterioration of the disease for which the corticosteroids were prescribed. Finally, hypersensitivity reactions to CS are truly rare and can have quite atypical presentations. Despite these diagnostic hurdles, it is clinically beneficial for treating physicians to maintain a high level of suspicion of this entity. There are a growing number of case reports describing allergic reactions to both systemic and topical CS, but few systematic studies have been conducted. In this article, we review the literature on corticosteroids hypersensitivity and explore the diagnostic and therapeutic challenges that physicians are confronted with when the possibility of corticosteroid sensitivity exists.

Epidemiology

The incidence of CS hypersensitivity varies depending on the study population. Patients with asthma may have a different incidence rate than those with inflammatory conditions or patients with dermatitis. Furthermore, those with a history of frequent exposures to steroids tend to have a relatively higher rate of hypersensitivity when compared to controls. Broadly, hypersensitivity reactions to steroids are divided into two categories: immediate reactions, typically occurring within 1 h of drug administration, and delayed reactions, which occur more than an hour after drug administration. The latter group is more common and will be discussed first.

Delayed Hypersensitivity Reactions to Corticosteroids

Allergic contact dermatitis (ACD) is the most common delayed hypersensitivity reaction. Indeed, there is a larger body of literature on CS-mediated ACD than the few case reports on immediate hypersensitivity reactions. Rates of allergy to topical steroids reportedly range from 0.5 to 5 % [5]. Lutz et al., while investigating the skin patch test results of 1,536 patients, found hypersensitivity to tixocortol pivalate (TV) in 45 patients [6]. Facial dermatitis was the most common (14 patients) manifestation. Of the 45 patients, 40 had another allergen identified on patch testing. Eighteen patients underwent further patch testing to an extended corticosteroid panel, and 14 demonstrated sensitivity to another steroid

agent. The 2.9 % prevalence of TV hypersensitivity in this US population is concordant with the range reported in Europe. Since TV and hydrocortisone belong to group A (which will be discussed in more detail below), TV is used in patch test as a representative of group A. According to a Danish study on patients who underwent patch testing for different kinds of dermatitis, the rates of delayed contact hypersensitivity were 2 % for all steroids together, 0.8 % for tixocortol-21-pivalate, 1 % for budesonide, and 1 % for hydrocortisone-17-butyrate [7]. Chronic dermatitis, including atopic dermatitis (AD) and leg dermatitis, were identified as significant risk factors for group A corticosteroid hypersensitivity. This increased incidence was most likely due to excess use of group A steroids as it is readily available as an over-the-counter (OTC) medication and is widely misused by patients with a chronic dermatitis. Indeed, one recent retrospective study of approximately 320 million visits to US physicians between the years 1989 to 2008 showed that hydrocortisone accounted for the second most commonly recommended OTC product at 16.9 % [8]. With regards to group B and D2 CS allergy, the duration of the skin condition rather than its etiology appeared to be associated with an enhancement of the risk of CS ACD hypersensitivity. One British study involving 1,562 patients with suspected allergic contact dermatitis revealed the rate of hypersensitivity to either betamethasone-17-valerate (BV) or clobetasol propionate to be 1 % (0.7 % for the former alone and 0.8 % for the latter alone) [9]. A skin patch study series by Abramson et al. on patients with allergic contact dermatitis to topical medications reported topical steroids as the second most common sensitizer (30 %), with TV the most frequently implicated culprit [10].

Inhaled and intranasal CS can cause delayed hypersensitivity reactions. Despite their widespread use, only a few reports about their sensitization potential have been published. Either the corticosteroids or added components such as preservatives can be causative and may result in allergic or irritant reactions, which can be relevant to clinical symptoms. Bennett et al. conducted a prospective study of 30 adult patients using inhaled or intranasal corticosteroids. The researchers used patch testing to determine the prevalence of allergic contact hypersensitivity to corticosteroids and common additives (propylene glycol and benzalkonium chloride) in inhaled and nasal corticosteroid preparations within their study population. Of the 30 patients, four (13 %) demonstrated a positive patch test result with probable clinical significance. Three of these cases (10 %) were considered to be a true allergic reaction, and one case (3 %) was an irritant reaction. Half of the allergic reactions were to a corticosteroid (budesonide), and half were to benzalkonium chloride, a common preservative in nasal preparations. The authors acknowledge that their study was too small to form a definitive conclusion [11, 12]. However, their study did highlight the importance of

considering CS hypersensitivity in patients whose symptoms worsen after initiation of therapy. In 2003, Kilpio and Hannuksela recruited 51 asthma patients with a history of an adverse reaction to their steroid inhaler and compared their skin patch tests results to 50 asymptomatic asthma patients with no such history. Two patients in the former group exhibited positive skin patch test reactions; one to BV, hydrocortisone-17-B (Hc-17-B) and budesonide, and the other patient to budesonide and Hc-17-B. The first patient had a history of developing widespread eczematous dermatitis whenever using BV. Fluticasone caused him oropharyngeal irritation, hoarseness, and shortness of breath. The second patient had experienced a severe rash after the fourth dose of inhaled budesonide. She had used various topical corticosteroids preparations for her atopic dermatitis without any adverse effects. None of the patients from symptom free group showed positive patch test results [13].

Immediate-Type Hypersensitive Reactions

Rarely, immediate-type systemic hypersensitive reactions can manifest after administration of oral, parenteral, or even intra-articular steroids. Data on prevalence of such reactions to systemic CS are rather sparse compared to the more commonly reported delayed-type reactions. As early as the 1950s, Kendall reported 20 systemic reactions occurring in a cohort of 2,256 patients who had received a total of 6,700 corticosteroid injections [14]. Dulloo et al. reviewed 213 children treated with intravenous CS for various rheumatologic conditions. Their study calculated the rate of anaphylaxis to be 0.5 % [15]. A more recent study has placed the estimated prevalence of steroid hypersensitivity after systemic administration at 0.3 % [16]. Unfortunately, the bulk of the available data regarding immediate-type reactions rely on case reports. The most commonly implicated corticosteroids causing anaphylaxis-like reactions are hydrocortisone, prednisone, and methylprednisolone.

Corticosteroid-induced bronchospasm is more often seen in asthmatics with a history of aspirin allergy [17–19]. In cases of worsening of asthma despite adequate treatment, corticosteroid-induced bronchospasm should be considered in the differential. The rates of hypersensitivity reactions are also higher in patients receiving chronic or recurrent doses of topical or systemic, especially parenterally administered, steroid therapy [20]. Most of these systemic reactions have been reported in adults.

Clinical Presentation of Reactions to Corticosteroids

Hypersensitivity to corticosteroids can present in various clinical forms, depending on the route of administration, duration, chemical structure, and quantity of drug. These

reactions can range from type I hypersensitivity reactions in the form of anaphylaxis to type IV delayed type hypersensitivity reactions that result from topical application of the drug to the skin. Other reactions include morphea, systemic contact dermatitis, maculopapular exanthematous rash, and rarely fixed drug eruptions, exfoliative dermatitis, Stevens–Johnson syndrome, generalized erythroderma, as well as acute generalized exanthematous pustulosis (AGEP). To further complicate matters, the drug itself may be innocent but rather the vehicle of its delivery is responsible for the adverse hypersensitivity reaction.

Clinical Presentation of Hypersensitivity Reactions to Corticosteroids

Ocular, Nasal, and Inhaled Corticosteroids

Allergic contact dermatitis is the prototype of a delayed type steroid hypersensitivity. Baeck et al. reviewed the data of patients who had previously reacted positively to corticosteroids over an 18-year time period, including their pertinent clinical histories, skin patch test results, and sensitization sources. Of the 315 subjects with hypersensitivity reaction to CS, 12 had allergic manifestations following nasal or inhaled corticosteroids, 11 of which were due to budesonide and one due to TV. Patients allergic to inhaled CS mainly presented with eczema around the nose, eyes, mouth with possible spreading to face, and neck [21]. In the same cohort of 315 subjects, 18 patients had presented with a delayed-type hypersensitivity reaction to CS-containing ocular preparations. These reactions included conjunctivitis, eczema of the face, eyelids, and periocular areas. The most sensitizing allergen was HC; however, most patients demonstrated multiple positive tests, not only to other CS but also to other active ingredients, preservatives, and vehicle components [22]. It is worth noting that in this study, 15 subjects with a delayed-type ACD reaction to topical CS denied any history of prior treatment with aerosolized CS. However, a more detailed history revealed that these subjects had been co-habiting and even caring for, patients with chronic respiratory conditions which required inhaled CS. Baeck and Goossens thus hypothesized that this cohort of patients had been sensitized by airborne exposure, possibly through inhalation and/or physical contact of CS allergen particles on the skin. The researchers concluded that exposure to inhaled corticosteroids, particularly budesonide, needs to be taken into account as a potential cause of primary sensitization and/or airborne allergic contact dermatitis [23]. Body sites typically involved in ACD to topical steroid include scalp, face, anogenital area, and lower extremities [24]. Evaluation of hypersensitivity to these agents is performed with patch testing. Cross-reactivity among topically administered corticosteroids is not uncommon and often can be

predicted on the basis of further patch testing and a standard classification system [25].

Reports of respiratory delayed-type IV allergic reactions to corticosteroid inhalers and nasal sprays in patients with asthma or allergic rhinitis are scarce. The local adverse effects of nasal corticosteroids have ranged from worsening nasal congestion, pruritus, burning, angioedema of lip, perioral dermatitis, and soreness of nose to perforation of the nasal septum [26]. Sohlenkamp et al. reported two cases of perioral dermatitis to CS nasal spray [27]. Inhalation of corticosteroids into the lungs has been reported to cause pruritus, erythema, perioral dermatitis, angioedema, and dysphagia [28, 29]. Cadinha et al. reported a case of a woman with asthma and allergic rhinitis who developed delayed upper lip angioedema and shortness of breath 24 h after commencing a budesonide inhaler [30]. Pitsios et al. reported two similar cases. The first was an atopic female who developed nasolabial angioedema and pruritis following budesonide nasal spray use. She also later developed oropharyngeal edema, erythema, and pruritis after starting a formoterol/budesonide inhaler for her asthma. The other case is an atopic female teenager who developed a pruritic rash around her nostrils after using a budesonide nasal spray. She experienced the nasal pruritis, intense nasal congestion, and facial edema when the same nasal spray was re-tried 1 year later. Patch tests were positive to budesonide on both patients [31]. Systemic allergic reactions reported following the use of nasal or inhaled corticosteroids have included eczematous lesions, predominantly on the face, sometimes with spreading to the trunk and flexural areas. There is one recent case report of inhaled fluticasone inducing rapid atrial fibrillation in a 15-year-old male which resolved after discontinuation of the medication [32].

Reactions to Topically Applied CS to the Skin

Hypersensitivity reactions to topical CS typically present as either a localized or generalized eczematous rash, with delayed-type ACD accounting for the most common manifestation. Patients with pre-existing AD are at particular risk of developing ACD to various topically applied medications, CS included. Liu et al. patch tested 641 children with AD against seven different topical treatments. Of the 40 patients who showed a positive patch result, one (2.5 %) was against tixocortol-21-pivalate and none against budesonide [33]. Skin barrier dysfunction, pH disruption, and the chronic inflammatory micro-milieu which characterizes atopic dermatitis and ACD to other topical medicaments can all predispose the patient to ACD against topical CS. In such cases, patients with AD or ACD may present with worsening skin condition after starting topical CS treatment. Gonul et al. patch tested 41 patients with ACD who did not respond to topical CS. Nine (22 %) of these patients tested

positive to either single or multiple CS. Other less common manifestations of topically mediated CS allergy include morphea [34] and pseudo-morphea as well as systemic contact dermatitis, maculopapular, and exanthematous rashes. Ruddell et al. reported the case of a 27-year-old female with a history of ACD to group A and group D topical CS, who developed a generalized exanthema within 24 h of receiving oral prednisone. Her patch tests were positive to group A, C, and D steroids. She tolerated oral triamcinolone [35]. Five years later, Liu et al. reported two additional cases. The first involved a 38-year-old patient with a severe local allergic reaction to inhaled budesonide whose skin testing was not only positive to group B steroids but also elicited a disseminated macular exanthema. The second case was a 38-year-old male who first had an ACD reaction to a topical steroid then a disseminated eczematous exanthema after oral prednisone intake [36]. Fixed drug eruptions, exfoliative dermatitis, and acute cutaneous postural reactions have also been reported in the literature, though thankfully they are quite rare. Kang et al. reported a 31-year-old Japanese woman who developed AGEF-like rash following topical application of hydrocortisone 17-butyrate 21-propionate [37].

Reactions to Systemic Corticosteroids

Reactions to systemic corticosteroids are typically anaphylactic or anaphylactoid (non-IgE-mediated) reactions presenting with generalized urticaria, wheezing, shortness of breath, angioedema, hypotension, and or abdominal pain. Walker et al. recently reported cases of two adult males who developed an anaphylactic reaction following intravenous administration of methylprednisolone sodium hemisuccinate and prednisolone sodium hemisuccinate [38]. These hypersensitivity reactions should be differentiated from deterioration of the underlying medical condition for which the steroids were originally prescribed; for example, allergic reaction to a steroid, especially parenteral form, could be misinterpreted as worsening of primary asthma exacerbation or the second phase of a food allergic reaction.

Samimi and Siegfried described a case of a 9-year-old female with lupus nephritis who developed cutaneous bullae and mucositis during treatment with intravenous methylprednisolone. The initial differential diagnosis included bullous lupus, but skin biopsy specimen findings supported a diagnosis of Stevens–Johnson syndrome. She was subsequently managed with intravenous immunoglobulin [39]. Polosa et al. reported a case of an anaphylactic reaction to oral prednisone in a 17-year-old with asthma and aspirin allergy [18]. More recently, Erdmann et al. reported the case of a 23-year-old female with atopic dermatitis who developed an anaphylactic reaction after starting oral prednisone. Her skin testing with a panel of CS confirmed an immediate type

reaction to several CS, including prednisone [40]. Sheth et al. reported a patient with aspirin allergy, asthma, and nasal polyps who developed bronchospasm following the administration of intravenous methylprednisolone sodium succinate during an acute asthmatic attack [17].

Nahum et al. reported three case reports of children with a hypersensitivity reaction to methylprednisolone sodium succinate [41]. Three patients (ages 5, 7, and 8 years old) with asthma who were treated with intravenous methylprednisolone succinate at the emergency department developed reactions which were initially attributed to their disease. Two of these children demonstrated a positive skin prick testing to methylprednisolone sodium succinate but not to other corticosteroids compounds, or to the succinate ester. The third patient underwent repeat skin prick tests to various corticosteroids 4 years after the adverse event, but his results remained negative. The authors concluded that methylprednisolone sodium succinate may cause anaphylactic or anaphylactoid reactions in susceptible children, which places an emphasis on the importance of physician awareness of such reactions.

Saito et al. reported on a patient who developed anaphylaxis following the intravenous administration of methylprednisolone sodium succinate during a renal transplant operation [42]. The patient's histamine and tryptase levels were found to be elevated after this event. Subsequent intracutaneous testing with methylprednisolone showed a strong positive reaction. To date, there have been a total of 14 documented cases of anaphylactic reactions following administration of methylprednisolone in renal transplant recipients. The latest case, as reported by Gelincik et al., described a 26-year-old male with Alport syndrome who developed anaphylaxis to methylprednisolone just before his renal transplant [43].

Lehman and Ott reported a case of a 2-year-old male who developed a hypersensitive reaction following intravenous administration of prednisolone-21-hydrogen succinate. The child's skin prick testing to the suspected CS agent showed a positive result. He did not react to prednisone, betamethasone, or dexamethasone. His fluorescence enzyme immunoassay analysis revealed no specific IgE antibodies against prednisolone-21-hydrogen succinate. However, the CD63-based basophil activation test (BAT) demonstrated a positive result. Additional incubation of basophils with the other CS compounds failed to elicit any significant response. The authors then performed an oral provocation test with betamethasone and a titrated intravenous dexamethasone challenge. As both drugs were tolerated with no complications, they were recommended for future treatment [44].

de Sousa et al. reported the cases of five male children with a history of immediate-type reactions to systemically administered corticosteroids. Their symptoms varied from diffuse urticaria and angioedema to anaphylactic shock

immediately after administration. In two cases, oral betamethasone was the suspected drug, oral prednisolone in the other two cases, and intravenous prednisolone in the last case. Four out of five patients underwent skin prick tests with various CS agents, including prednisolone (both oral and parenteral) and oral betamethasone, if these results were negative, an intra-dermal skin testing followed at increasing concentrations. Skin test results were positive in the four cases, thus suggesting an immunoglobulin E-mediated reaction as the underlying mechanism [45]. Eda et al. reported two patients with a history of severe cow's milk allergy who had developed an immediate-type reaction following parenteral administration of methylprednisolone sodium succinate. Further investigation with skin prick tests revealed that this particular batch of medication has been contaminated with beta-lactoglobulin during its preparation [46].

Other Routes of Administration

Karsh and Yang reported a case of anaphylaxis to intra-articular injection of triamcinolone in a 75-year-old male. His prick skin tests were positive to triamcinolone and negative to lidocaine, methylprednisolone, and hydrocortisone [47].

Pathogenesis

Cortisol readily penetrates the cutaneous corneal layer because of its low molecular weight and high lipophilicity, two factors which render it an ideal contact allergen [48]. The structure of corticosteroids is illustrated in Fig. 1. Bundgaard et al. have demonstrated that the C21 position of the hydrocortisone molecule in aqueous solution is degraded to a steroid glyoxal. Glyoxals can bind covalently the guanidino groups of arginine, in turn forming a stable hapten with cutaneous or serum proteins and thus creating an immunogenic agent. This haptenized steroid, especially its ring structures, serves as an allergenic substance to induce a hypersensitivity reaction in susceptible individuals upon re-exposure (Fig. 2). Topical preparations containing hydrocortisone in equimolar conditions could influence the affinity of its binding to arginine and thus the promotion of cell-mediated sensitization to topical CS. An alkaline environment could also encourage cortisol oxidation and degradation, an effect which leads to a higher rate of steroid glyoxal generation and binding to available arginine. Usually, healthy cutaneous pH is maintained at approximately 5.5. However, in more sweat-prone areas such as the axilla and perineum, that value can rise to as high as 8. Other conditions that promote the alkalinity of the skin surface include cutaneous bacterial infections, eczema associated with areas of venous stasis, and both irritation-type and allergic-type contact dermatitis. Indeed, the influence of skin surface

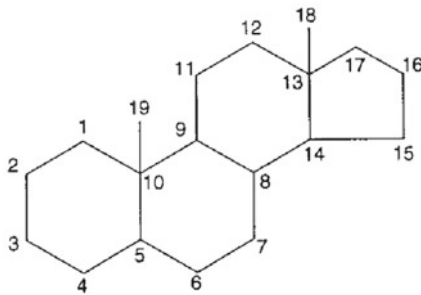
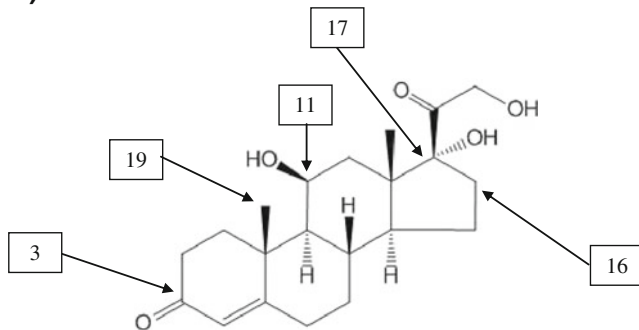
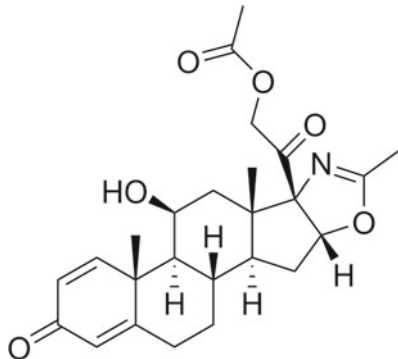
A) The numbering system of corticosteroids**B) Cortisol****C) Deflazacort**

Fig. 1 Structure of steroids. **a** The numbering system of corticosteroids. **b** Cortisol. **c** Deflazacort

pH on the allergenicity of topical steroids may explain the particular increased incidence of CS-mediated ACD in patients with stasis dermatitis, perineal dermatitis, and chronic leg ulcers (Table 1).

Aside from glyoxal formation, the generation of cortisol–transcortin or cortisol–albumin conjugates was also been implicated in the etiology of steroid hypersensitivity. Synthetic CS administered in large doses can haptenize with these circulating serum proteins, which in turn will create stable, immunogenic allergens. Patients at particular risk include those with asthma, hypersensitivity to acetylsalicylic acid or to

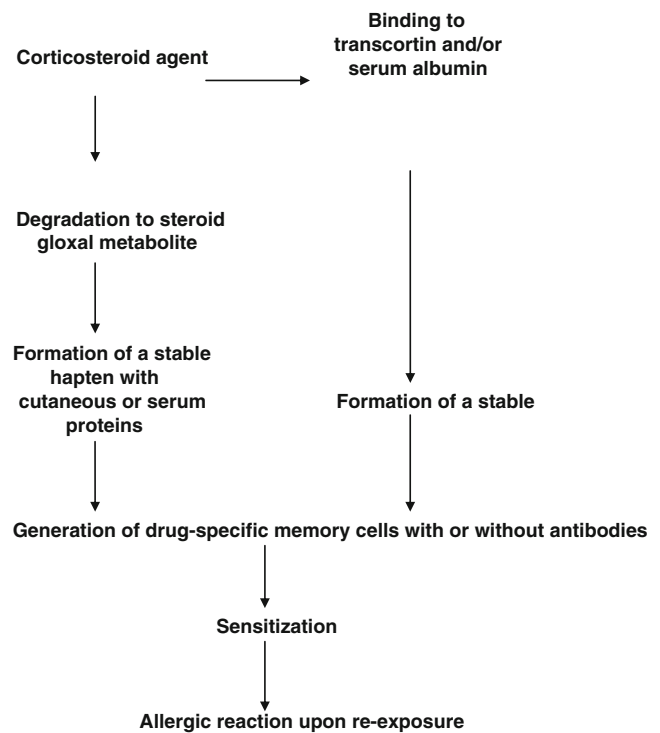


Fig. 2 Mechanism of steroid hypersensitivity

other nonsteroidal anti-inflammatory drugs, and a history of nephritis or renal transplantation [48]. In addition, patients requiring frequent and/or high-dose boluses of CS, such as patients with systemic erythematosus lupus, rheumatoid arthritis, and psoriasis, were also found to be at increased risk regardless of the mode of steroid delivery (systemic, intra-lesional, or topical). As confirmed by prior dermatological studies, percutaneous absorption can lead to concealed or underestimated sensitization.

A differentiation must be made between allergic and non-allergic CS-mediated hypersensitivity. The former involves specific IgE or IgG antibodies or specific

Table 1 Risk factors associated with corticosteroid hypersensitivity

Drug factors
Ability of the corticosteroid to bind arginine
Host factors
Increased skin alkalinity (due to sweat, cutaneous infections, venous stasis, occlusions, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis)
Hypersensitivity to NSAIDs
History of repeated use of high-dose systemic CS boluses (e.g., such as in asthma, nephritis, and renal transplant)
History of frequent corticosteroid use
Co-sensitization to other topical medicaments (neomycin or chlorhexidine)

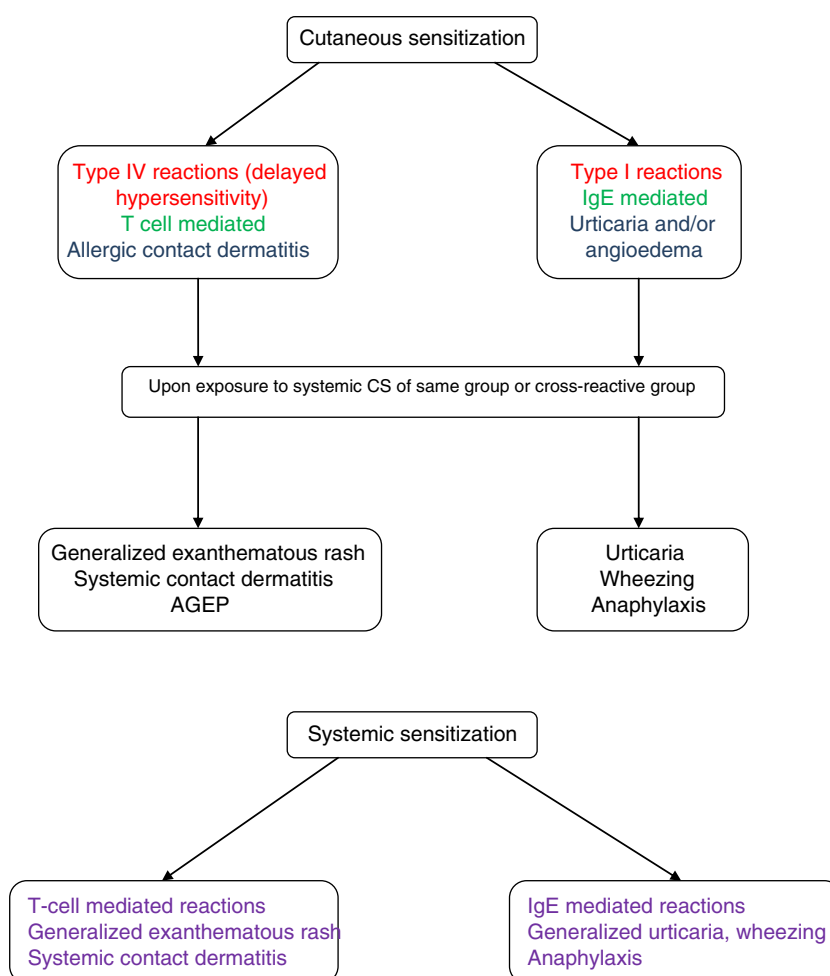
T-lymphocyte subset populations that mount a response. Allergic contact dermatitis is largely a type IV, T-cell-mediated reaction. The available evidence suggests that allergic reactions to systemically administered CS are probably mediated by specific IgE antibodies. Sensitization takes place from prior exposure, leading to the development of drug-specific antibodies or antigen-specific memory T-lymphocytes. Re-exposure to the CS agent precipitates an allergic response (Fig. 3). Non-allergic hypersensitivity reactions to CS, on the other hand, involves very little of the adaptive immune system. Instead, exposure to CS compounds is believed to directly activate components of the innate immune system, including mast cells, basophils, and the complement cascade. CS-mediated inhibition of the cyclooxygenase pathway has been suggested as the underlying mechanism. Insofar as any clinical relevance, it is generally recommended to perform an incremental challenge with the suspected culprit drug despite a negative skin prick and intradermal tests, immunoCAP assays, skin patch, and basophil activation test since all these results only

account for allergic hypersensitivity reactions and not the non-allergic types.

The pharmaceutical industries offer a wide myriad of CS with different methods of administration. Sensitization to these agents can occur through either topical or systemic exposure. Initial sensitization through one route does not mean that the patient will be spared a reaction if re-exposure occurs through an alternative route. It is possible to manifest a hypersensitivity reaction to a systemically administered CS even though previous sensitization has occurred by mere topical application. Nevertheless, the most commonly implicated route of CS sensitization remained through cutaneous exposure. Other less typical routes cited within the literature include respiratory (intra-nasal and inhaled), digestive, and intra-articular. Sensitization through parenteral administration of a CS is fortunately rare.

In addition to possible adulteration with other protein allergens, it would be helpful to remember that preservatives, suspending agents, and additives can also cause an allergic reaction. The discussion of allergic reactions to

Fig. 3 Evolution of clinical sensitization



these components is beyond the scope of discussion within this article. Nevertheless, to prevent the false implication of an important medication such as CS, testing for other components of the preparation should be attempted, or at least entertained, before burdening the patient with a “steroid allergy” diagnosis. Patterson et al. reported the case of a patient who developed an anaphylactic reaction shortly after receiving injected triamcinolone acetonide. Skin prick testing and serologic testing for allergen-specific IgE antibodies were positive for carboxymethylcellulose, a suspending agent used in injectable triamcinolone, but negative to other carboxymethylcellulose-free steroid preparations [49]. Laing et al. reported a similar allergic reaction in a patient who received an intralesional steroid injection containing carboxymethylcellulose [50].

The Cross-Reactivity Spectrum of Corticosteroids Based on Molecular Structure

The Coopman (or ABCD) classification system, based on the 1989 publication on steroid allergy of S. Coopman et al., divides the various CS into four groups of cross-reacting compounds [51]. This classification was further validated by Goossens et al. based on skin patch test results obtained from a large cohort of corticosteroid allergic patients (Table 2) [52].

These data on true allergic cross-reactivity among topical CS are provided by patch testing with compounds to which sensitive patients have never been previously exposed. The

cross-reactivity of CS compounds has practical consequences for the identification of those CS most frequently responsible for sensitization, as well as the choice of which agent to use for diagnostic testing. In general, the most positive reactions have been observed to group A, group B, and those compounds belonging to sub-group D2. This latter group in turn shows a significant rate of cross-reactivity among its own members as well as to group A compounds and budesonide (group B). On the other hand, group C and those of the sub-group D1 produce very few allergic contact reactions. Furthermore, compounds of group C and group D1 exhibit minimal cross-reactivity with other steroid groups. There is a well-established cross-reactivity association between tixocortol pivalate and hydrocortisone. Therefore, the former is often used to demonstrate a cutaneous allergic reaction to the group A compounds. Budesonide detects a different pattern of corticosteroid hypersensitivity. It is involved in cross-reactivity not only with members of its own group (group B) but also with some members of group D2.

Even though less is known about the classification and cross-reactivity patterns of systemic steroid preparations compared to topical preparations, the tolerability of alternative halogenated CS, such as betamethasone and dexamethasone, in patients who have previously suffered immediate hypersensitivity reactions to succinate esters of hydrocortisone or methylprednisolone has been confirmed in two studies [53]. Nakamura et al. conducted a study on seven adult patients with asthma, each of whom had a history of

Table 2 Classification of corticosteroids

Classification	A	B	C	D	
				D1	D2
Characteristics	No substitution on the D ring except a short chain ester or thioester on C21	Acetonides	Methylation on C16	Methylation on C16 Halogen substitution	No methylation on C16 No halogen substitution Side chain ester on C17 Possibly side chain ester on C21
Examples	Hydrocortisone	Triamcinolone acetonide	Betamethasone	Clobetasone-17-butyrate	HC-17-propionate
	Prednisolone		Dexamethasone		HC-17-butyrate
	Methylprednisolone	Fluocinolone acetonide	Desoximetasone	Clobetasol-17-propionate	Methylprednisolone aceponate
	And their ester acetates, sodium phosphates, and succinated	Halcinonide	Fluocortolone	Beclomethasone dipropionate	Prednicarbate
	Cortisone acetate	Desonide		Betamethasone valerate	Diffuprednate
	Prednisone	Fluocinonide		Betamethasone dipropionate	
	Tixocortol pivalate ^a	Budesonide ^a			

^a Used in patch tests

systemic anaphylactic reaction following intravenous corticosteroid administration for the treatment of acute asthma. Clinical characteristics were studied retrospectively on the basis of their available medical records. Systemic anaphylactic reactions to intravenous corticosteroids occurred in severely atopic asthmatics with a history of previous exposure to parenteral corticosteroids, irrespective of age and gender. Aspirin-intolerant asthmatics were identified in only three cases. In all seven subjects, anaphylactic reactions were induced following intravenous administration of succinate-containing corticosteroid preparations, i.e., hydrocortisone and methylprednisolone. Administration of phosphate-containing corticosteroids, i.e., dexamethasone and betamethasone, was safe and resulted in an amelioration of anaphylactic reaction. Immunological examination with skin tests suggested that these anaphylactic reactions were indeed IgE-mediated [54].

The most often implicated systemically administered CS are hydrocortisone and methylprednisolone, which belong to group A according to the ABCD classification, and within which cross-reactions may be observed. Contrary to these findings, however, Venturini et al. [55] conducted a study on seven cases of immediate hypersensitivity to systemic CS and were unable to prove the existence of cross-reactions between members of the same CS group. There are case reports as mentioned in the next section, of patients with a hypersensitivity reaction to methylprednisolone who have tolerated hydrocortisone even though both drugs belong to group A [56]. The ABCD classification with D1, D2 sub-classification is useful in directing the search for a replacement agent, but cannot replace a systematic, individualized evaluation of each patient's sensitization and tolerance profile. There are newer corticosteroids as well, such as deflazacort, that do not fit into the A, B, C, D classification system.

Diagnosis and Evaluation of Hypersensitivity to Corticosteroids

A detailed evaluation with particular emphasis on CS drug history, the chronology of its administration, and symptom development helps the clinician establish the presence of a true hypersensitivity reaction to the suspected drug and choose the safest alternative. This evaluation becomes especially important in high-risk groups such as patients with asthma, autoimmune or inflammatory diseases, and other immunological conditions where steroids are a life-saving treatment. The assessment should be done when the patient's underlying condition is in a quiescent state. Choosing an alternative CS is not only paramount to the patient's safety but also ameliorates the worry of developing an allergic, and potentially fatal, steroid hypersensitivity

reactions. Often other agents are available as well, and the risk–benefit ratio of switching to a newer alternative such as a biologic should be considered in the management of these patients [4, 57–60].

There are unfortunately no standardized tests to confirm steroid allergies. Skin prick, intradermal and patch tests, immunoCAP, lymphocyte transformation test, and BATs are useful in evaluation patients with steroid allergy. However, in a patient with a confirmed immediate-type hypersensitivity to CS, it is still not possible to predict which CS might be tolerated by exclusively relying on clinical presentation or results of skin and in vitro testing. Therefore, incremental CS challenges under standardized clinical conditions remain essential in order to facilitate a patient-tailored emergency treatment and to avoid severe reactions in these patients (Fig. 4).

Aranda et al. compared four patients who had an immediate allergic reaction to methylprednisolone with ten controls [56]. Skin prick and intradermal testing were performed using methylprednisolone, hydrocortisone, and dexamethasone. Those with a negative result next underwent a drug provocation test to confirm the diagnosis and assess for any cross-reactivity. BAT and immunoCAP were also performed to further affirm the presence of an underlying IgE-mediated response. Three subjects were diagnosed by a positive skin test with methylprednisolone. Of those patients, two were identified by prick skin testing and one by intradermal testing. All four patients exhibited good tolerance to hydrocortisone and dexamethasone. BAT was positive for only methylprednisolone in those patients with positive skin tests, with all

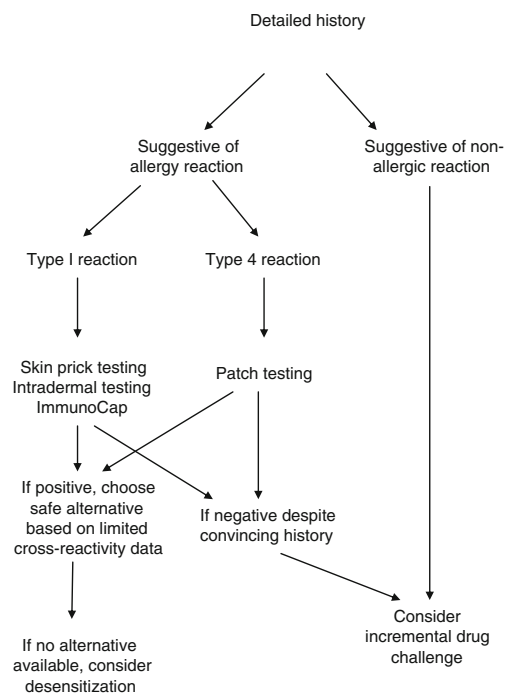


Fig. 4 Algorithm for the approach to corticosteroid hypersensitivity

patients being negative for the other two CS agents. Two patients demonstrated an elevated immunoCAP level to methylprednisolone. Skin testing, immunoCAP, and BAT are useful to confirm the IgE-mediated hypersensitivity reactions. One of the four patients was skin test negative and diagnosed by a drug provocation challenge. Aranda et al. theorized that this patient probably had suffered a non-IgE-mediated reaction. These findings support the recommendation of performing a drug provocation test in all patients with typical allergic reaction but negative skin tests, BAT, and/or immunoCAP.

Management

Use of Alternative Agents

Given the ubiquity of CS administration as first-line treatment in a variety of allergic and inflammatory and immunological conditions, a steroid hypersensitivity presents a real challenge to the treating physician. Lee-Wong et al. reported a case of successful systemic hydrocortisone desensitization in a patient with history of CS hypersensitivity and radiocontrast-induced anaphylactoid reaction, which required cardiac catheterization for unstable angina. Firstly, hypersensitivity to different CS was determined with skin test. Desensitization to HC was started at a diluted strength of 1:100,000 and at a dose of 0.001 mg. Each dose was given over 5 min. Escalated doses were given every 15 min. A total cumulative dose of 256 mg (75 ml) of HC was given over a 4.5 h period. The patient developed mild itching and erythema between third and fourth dose that were promptly resolved with diphenhydramine. After completing the protocol, the patient was given 200 mg intravenous HC every 4 h. Then the patient was premedicated with HC 200 mg and diphenhydramine 50 mg IV an hour before the cardiac catheterization. The patient tolerated radiocontrast material during the catheterization without any adverse reaction.

On a more clinically practical level, however, a patient with such a reaction should undergo evaluation testing for alternative preparations to determine which could be safely administered if or when a steroid treatment is required again. Ventura et al., in an effort to identify safe alternative CS for emergency use in patients with a history of hypersensitivity to systemic CS, recruited ten steroid-allergic patients. Skin prick tests to hydrocortisone and methylprednisolone were negative in all ten patients, but eight demonstrated a positive intradermal skin test result. Intradermal tests to betamethasone and dexamethasone were negative in all ten patients. Oral challenge tests to dexamethasone ($n=10$) and deflazacort ($n=6$) were negative in all patients. The authors concluded that betamethasone and deflazacort might be safe alternatives in patients with a hypersensitivity reaction to

other corticosteroids [53]. This finding becomes more pertinent in patients with a higher rate of steroid hypersensitivity, such as those with bronchial asthma.

A study by Qureshi et al. demonstrated that in a pediatric population, two doses of oral dexamethasone were as efficacious as five doses of oral prednisone with fewer side effects [61]. This observation raises the question that if dexamethasone and betamethasone are possibly less allergenic, should physicians be employing them in place of relatively higher allergenic CS such as budesonide, hydrocortisone, and methyl prednisolone, especially in such high-risk patients. More studies would certainly be needed to better define the allergenicity of different groups of steroids.

Discussion

CS remains a cornerstone of the management of allergic and inflammatory conditions. Paradoxically, CS themselves can trigger a hypersensitivity reaction with a wide variety of underlying pathophysiologic mechanisms as the cause, ranging from allergic to pseudoallergic, immediate to delayed type. While all routes of sensitization have been reported (nasal, aerosolized, parenteral, oral), the cutaneous route is both the most common and probably the most pertinent given the easy availability of such agents since the Food and Drug Administration-approved low-potency topical CS medications in 1979. Despite their widespread use, allergy to CS remains rarely reported. Whether this is because it is truly an uncommon condition, or is under diagnosed and therefore unrecognized, is unclear. Indeed, the exact incidence of CS hypersensitivity is difficult to estimate and is limited to case reports and small clinical studies. These studies indicate that patients with stasis dermatitis or atopic dermatitis have a higher incidence, as skin barrier dysfunction increases the risk of sensitization and subsequent hypersensitivity reactions upon re-exposure. Other contributing factors to CS allergy development include the site of topical application, such as the anogenital region or legs. The frequency of exposure to CS has also been associated with increased risk of hypersensitivity, as observed in asthmatic patients requiring repeated CS boluses for disease exacerbations. To further complicate matters, other ingredients within these topical medications, such as neomycin and emollients, can also co-sensitize at risk patients to CS.

CS allergy is not typically drug-specific. Thus, a patient sensitized to one agent is at risk of exhibiting hypersensitive reactions to other CS due to either co-sensitizations or cross-reactivity of these compounds, especially if they are members of the same family. All routes of sensitization, including cutaneous, can lead to systemic reactions. Therefore, a patient with contact dermatitis to one particular topical CS should avoid both topical and systemic CS from the same group.

Though rare, CS hypersensitivity can have deleterious consequences for the patient and adversely affect his or her management, leading to poor quality of life, limitation of treatment options, increased morbidity, and even mortality due to suboptimal disease control. A high degree of clinical suspicion is therefore warranted. Allergic contact dermatitis to steroids should be considered when cutaneous symptoms worsen despite topical CS therapy. Since inhaled and systemic CS can potentially cause hypersensitive reactions, it is reasonable to include CS hypersensitivity in the differential of an asthmatic patient whose symptoms worsen after initiation of therapy. Nevertheless, it can be challenging and frustrating for the clinician to distinguish between a hypersensitivity reaction and deterioration of the inflammatory disease for which the CS were prescribed. This diagnostic challenge emphasizes the importance of a thorough evaluation to identify the culprit drug and find a safe alternative for the patient. Choosing an alternative steroid agent is not only paramount to patient safety but also ameliorates the worry of developing an allergic, and potentially fatal, steroid hypersensitivity reaction. This evaluation becomes particularly significant in high-risk patients where steroids are a life-saving treatment.

Avoiding topical steroids as treatment modalities for certain dermatological conditions such as xerosis, psoriasis, and cosmetic and occupational ACD and instead focusing on dry skin care strategies, application of barrier methods, and avoidance of contact allergens might lessen the risk of CS hypersensitivity, especially in high-risk groups. If CS is needed, choosing a less allergenic CS may benefit these patients.

Amid this discussion of the unlikely possibility of type I and type 4 hypersensitivity to steroids, it should not be forgotten that corticosteroids may have much more common and much more severe adverse reactions that are not allergic in nature, including diabetes, hypertension, osteonecrosis, osteoporosis, suppression of the HPA axis, cataracts and glaucoma, and growth retardation in children. These side effects of steroids present a much more significant indication for close monitoring of the use of this very effective, but potential harmful, class of medications. The use of newer medications such as biological may be steroid sparing, but this is a new frontier and the potential adverse reactions of newer medications are not clearly elucidated as well.

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