

Review article

Allergic hypersensitivity to topical and systemic corticosteroids: a review

Corticosteroids, which are potent anti-inflammatory and immunomodulator agents used in the treatment of various inflammatory diseases including allergic diseases, can in some cases produce immediate or delayed hypersensitivity reactions. This review summarizes the epidemiological and clinical characteristics of such reactions, including related diagnostic issues. It also presents a detailed analysis of the proposed immunological mechanisms including underlying cross-reactions.

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The therapeutic properties of corticosteroids (CSs) were first demonstrated by Edward Kendall and Philip Hench in 1948 (1). During the 1950s it was discovered that hydrocortisone, a natural glucocorticoid hormone, could reduce inflammation and proliferation in some skin disorders (2). Chemical modifications of this basic hormone soon gave rise to multiple CSs of varying strength, each with its own specific properties. In addition to their basic role in the treatment for inflammatory skin pathologies, CSs are also used in emergency medicine and in several internal diseases. Corticosteroids have an anti-inflammatory effect, which is mainly related to the inhibition of transcription of several pro-inflammatory cytokines/mediators. Other factors contributing to their anti-inflammatory and immunosuppressant properties include the apoptosis of basophils and the inhibition of adhesion molecule expression on the surface of endothelial cells (3). It may therefore appear to be paradoxical that CSs, potent anti-inflammatory agents and immunomodulators used in the treatment of allergic manifestations (in the broad sense), are capable of producing

immediate or delayed allergic hypersensitivity (AHS) reactions. The first documented allergic reactions to CSs, following local application and injections of hydrocortisone, were described towards the end of the 1950s (4–6).

Diagnosing an allergic reaction to CSs remains a challenge for clinicians. Its clinical presentation is frequently atypical and tests may be difficult to interpret. Moreover, its frequency is undoubtedly under-estimated. While knowledge of delayed hypersensitivity as a secondary effect of topical CSs (allergic contact eczema) is improving, little is known about immediate and delayed reactions to systemic CSs. It is critical to address such reactions, as appropriate diagnostic work-up should determine potential replacement agent(s) that can still be tolerated by the patient.

Allergic and nonallergic hypersensitivity (AHS-NAHS)

Drugs are xenobiotics that interact with many cellular activation systems when carrying out their therapeutic

effects. Adverse drug reactions are grouped into two categories: those that are predictable, common, and related to the pharmacologic actions of the drug (Type A reactions); and those that are unpredictable, uncommon and usually not related to the pharmacologic actions of the drug (Type B reactions) (7). The latter include AHS and NAHS. These reactions are sometimes difficult to differentiate and involve different mechanisms. However, differentiation of these two kinds of drug intolerance is important as AHS is rare but can be life-threatening while NAHS is frequent, can sometimes be severe and in exceptional cases, can be fatal (8, 9).

Allergic hypersensitivity

These reactions are because of specific immune effectors, antibodies and/or T lymphocytes. Allergic hypersensitivity reactions require a prior sensitization to the drug, in order to develop an adaptive immune response with production of drug-specific antibodies (IgE or IgG) or T lymphocyte (CD4+ or CD8+). Allergic reactions can be classified, according to Gell and Coombs, into four types of immune reactions: Type I, immediate-type hypersensitivity reactions (immediate AHS – IAHS) because of IgEs, Type II and Type III, cytotoxic and immune complex reactions because of IgG or IgM antibodies, and Type IV, delayed-type hypersensitivity (delayed AHS – DAHS) because of CD4+ or CD8+ T-cells (7, 8). The Type IV reactions were further subclassified by Posadas and Pichler (7) into four subtypes (IVa–IVd) based on the clinical, immunohistochemical and functional heterogeneity of certain drug allergies. Indeed, T-cells have been found to differ in the cytokines they produce, which results in distinct types of immune defence.

A suspected AHS is diagnosed by demonstrating the presence of specific IgE or T-cells through *in vivo* or *in vitro* tests. The *in vivo* tests are mainly 'skin prick' test and/or an early-reading intradermal reaction (IDR) test in cases of IAHS and 'patch test' and/or a late-reading IDR test in cases of DAHS. *In vitro* diagnosis may include the identification of basophil activation/degranulation and IgEs specific to the drug for IAHS (10, 11) and lymphocyte transformation test (LTT) and IFN-gamma enzyme-linked immunospot assay (ELISPOT) for DAHS (12–14). Biological diagnosis of a DAHS reaction has made significant progress in recent years thanks to the work of Rozières et al. (12) and Pichler et al. (14). These researchers have studied various means of detecting specific T-cells to a given drug (particularly beta-lactam antibiotics). However, because of technical issues in particular (e.g. standardization of the reagents used), validation of these tests for routine clinical use remains difficult and at present, their use remains restricted to specialized clinical centres.

Nonallergic hypersensitivity

These reactions are much more frequent than AHS and are referred to as pseudo-allergies, false allergies, or drug intolerance. Unlike AHS reactions, they are not as a result of specific immune responses. Such reactions involve direct activation of the innate immune system (mast cells/basophils, complement) and do not involve specific antibodies or T-cells. Thus, NAHS may occur after the first application or administration of the drug and does not require prior sensitization. *In vivo* and *in vitro* tests are negative in this setting.

Sensitization routes

There is a huge variety of CS molecules and many ways of administering them. Both local and systemic treatments are possible and either mode can sensitize the patient and lead to a specific immune reaction. It is important to make a distinction between the original sensitization route and the observed secondary reactions to topical or systemic administration of a CS; these are not necessarily linked. A patient who reacts to a systemically administered CS, for instance, may have already been sensitized to this agent (or another chemically related agent) by previous topical use – or vice versa.

The most common sensitization route is through cutaneous use (15). Locoregional routes including respiratory (nasal or mouth inhalation), digestive and intra-articular administration have been less frequently implicated. Sensitization related to systemic administration of a CS, of which the intravenous route is the most common, occurs even less frequently (15, 16).

Factors influencing sensitization to CSs

Topical route

Patients who suffer from a long-term dermatological disease are at higher risk of sensitization when treated by topical CSs: these include chronic eczema, stasis dermatitis, chronic ulceration, chronic actinic dermatitis, facial, anogenital, and hand and foot dermatitis (17). Changes to the skin barrier and/or a local pro-inflammatory environment (favouring and priming antigen-presenting cells such as Langerhans cells) are the most likely determining factors.

It is not clear whether atopy represents a risk factor for the development of a CS allergy, or whether observation of such allergies might be due to a selection bias because this group of patients is more likely to receive CSs. Those patients who are allergic to a CS often exhibit co-sensitization to multiple allergens (e.g. preservatives, excipients and antibiotics). Degreef and Doooms-Goossens (18) demonstrated that 82% of their CS-allergic patients were

also sensitized to at least one other allergen. Not unexpectedly, contact allergy to CSs is only rarely occupationally induced (19).

Systemic route

The risk factors for developing sensitivity to systemic CSs have not been studied. It seems, however, that such reactions occur more frequently in asthmatic subjects (20, 21) and in patients regularly treated with systemic CSs (e.g. in the case of a missing or transplanted kidney) (22) than in other subjects. However, in these cases, it is difficult to determine whether the higher incidence of allergies observed is due to increased susceptibility, or to greater exposure to CSs.

Other factors such as hypersensitivity to salicylic acid might also constitute risk factors (23); neither can genetic predisposition to CS allergies be excluded (24, 25).

Prevalence of allergy to CSs

According to the literature, the prevalence of allergic reactions to CSs is extremely variable. Several factors such as regional differences in prescribing habits (i.e. the types of CSs commonly prescribed and the number of prescriptions given out), awareness of topical CS allergy among medical professionals, patient selection and referral, and diagnostic procedures, may have an influence.

Topical CSs

The literature reports that the frequency of CS allergy following topical application ranges from 0.2% to 5% or more (3, 17, 26, 27). Despite the wide use of inhaled CSs, very few cases of asthmatic patients experiencing allergic reactions have been reported (27, 28). Isaksson et al. (29), who examined patients with asthma or allergic rhinitis who were treated with tixocortol pivalate, observed a CS sensitization rate of 1.4%. Among nonasthmatic patients, however, the rate of sensitization was 0.9%, and the difference was not statistically significant. Malik et al. (30) were the first to evaluate the incidence of CS allergies in patients with digestive tract inflammation who were treated with steroid enemas. Of 44 patients, 9% were tested positive for one or more CS.

Systemic CSs

Allergic reactions following systemic administration of CSs have rarely been reported in the literature and most often concern isolated cases. In 1998, Klein-Gitelman et al. (31), in a cohort study of 213 children treated with intravenous CS for various rheumatological conditions, estimated the rate of allergic reactions to be 0.1% (for approximately 10 000 doses of glucocorticosteroid), most being of the immediate type. Other authors have

estimated the prevalence of such reactions at 0.3% (32). About a hundred publications have reported immediate reactions after oral or parenteral administration of CSs, the allergic nature of which was not always proved, while the prevalence of systemic contact dermatitis or systemic allergic dermatitis (33) to CSs has not been examined.

Clinical presentation

Recognizing CS allergy can be difficult, as its clinical presentation tends to be neither specific nor spectacular: the clinical signs are usually minor, or display a completely atypical chronology, which is due to the anti-inflammatory properties of the CS. As mentioned by Le Coz (34), the clinical manifestation of such reaction depends on two competing effects which are of variable intensity and offset in time: the immunological allergic response and the pharmacological 'anti-allergic' effect.

Type I and Type IV are the most frequent allergic reactions observed with CSs. IgGs (Type II); immune complex (Type III) associated reactions, although possible, have never been reported.

Allergic contact eczema following topical application of CSs is by far the most common form of delayed hypersensitivity. It may also be important to distinguish clinical symptoms according to the type of reaction (immediate or delayed) and the CS administration route (local or systemic). Table 1 summarizes the clinical aspects associated with each administration route and Fig. 1 illustrates various clinical aspects.

Diagnostic testing

In vivo tests

Delayed AHS. Type IV hypersensitivity can be identified by skin tests, mainly 'patch' tests.

Agents tested. The principal markers for CS contact allergy are tixocortol pivalate (although not for skin use) (69, 70), budesonide (17, 71), and hydrocortisone 17-butyrate (72), the first two having been introduced to the European baseline series in the early 2000s (73). A slight difference between the sensitization rate to tixocortol pivalate (2–5%) and to budesonide (1–2%) is reported (3, 17, 26), but taken together, these two allergens are said to detect nearly 90% of CS-allergic patients (74), although this percentage depends on the number of patients tested and the CSs used to screen for contact allergy. The other CS preparations used by the patient should, however, also be tested, along with all other ingredients.

Certain authors have proposed using a mixture of tixocortol pivalate, budesonide, and hydrocortisone 17-butyrate to detect CS allergy (75). However, a

Table 1. Allergic hypersensitivity to CSs: clinical presentation

Locoregional administration routes					
Cutaneous	Ophthalmologic	Respiratory			Systemic administration route Oral/Intravenous/Intramuscular
		Digestive	Nasal inhalation	Oral inhalation	
A chronic dermatosis which responds poorly or not at all to treatment, recedes very rapidly when the treatment stops, or grows worse following the application of a topical CS (35)	An ocular pathology which does not improve when treated with a CS-based collyria or unguent	A digestive pathology (BD) which improves very little or not at all after steroid irrigation (30, 44)	Eczematous eruption around an orifice (nostrils, nose, lips), with possible locoregional spreading (eyelids, cheeks, neck, thorax) (27, 45–47)		A pre-existing dermatosis that fails to improve or worsens after systemic CS treatment.
Chronic eczematous eruption (35)	Conjunctivitis (43)	Increased diarrhoea	Pruritus, dry or burning sensation (46, 47)		
Steroidal rosacea, perinasal dermatitis, perioral dermatitis (35, 36)	Eczema or oedema of the eyelids, periorbital eruption	Local irritation	Nasal congestion (29)	Erythema and/or oedema of the buccal mucosa (46, 49)	Generalized erythematous, macular, maculopapular, papulo-vesicular, pustular, purpuric or eczematous eruptions (6)
Chronic eczema, irritant dermatitis on the hands and/ or feet (35)	Pruritus, dry or burning sensation		Nosebleeds (29)	Contact allergy stomatitis (46, 47, 50)	Erythroderma (61)
Purpuric eruption (37)			Inflammation of nasal fossae and/or sinus cavity (29)		Baboon syndrome (62)
Eczematous eruption at the periphery of the treated zone ('edge effect') (34–36)			Chronic rhinitis unrelieved or aggravated by topical CSs (29, 46)	Odynophagia/dysphagia (46, 49)	Oedema of the eyelids (63, 64)
Eruption of erythema multiforme (38–40)			Perforation or ulceration of the nasal septum (48)		Angioedema
Genital oedema (38, 41)			Lack of improvement or aggravation of a respiratory pathology treated using inhaled CSs		Generalized urticarious eruption (5, 65)
Acute eczema (38)			Worsening of the bronchial obstruction (51)		Asthma attacks or bronchospasms in asthmatic subjects (5, 66)
Oedematous eruptions (40)			Severe asthma attack (51)		General symptoms (e.g. pruritus, vertigo, shaking, malaise, angina, bronchospasm, nausea, vomiting, abdominal pain, melaena) (64, 67)
Cutaneous lesions at some distance from the application zone (37, 38)			Marked reduction of FEV1 (51–53)		Shock and cardio-respiratory failure (68)
Photo contact allergy (42)			Bronchospasm, bronchoconstriction (52, 53)		
			Generalized maculo-erythematous or eczematous eruption (54)		
			Diffuse pruritus (29)		
			Urticaria, angioedema (29, 55)		
			Allergic reaction in subjects not themselves treated by inhalers, but responsible for or living with patients who use inhalers regularly (56)		

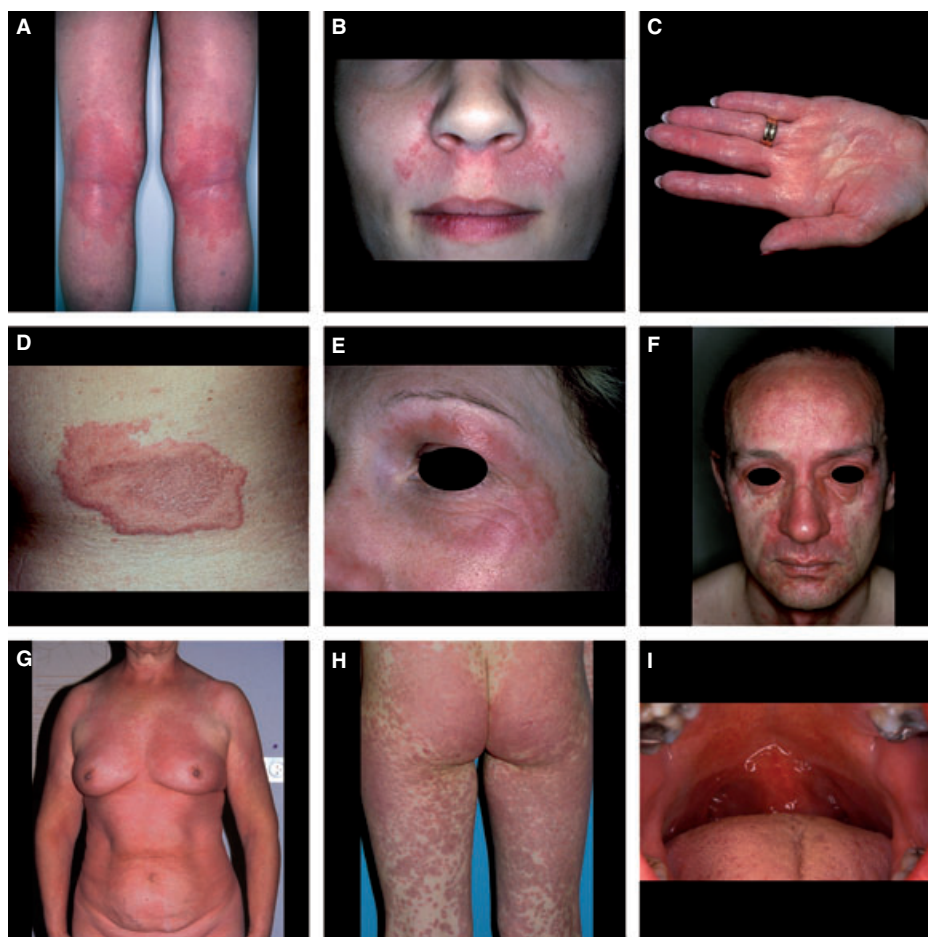


Figure 1. Illustrates various clinical aspects.

multi-centre European study has shown that more than 50% of patients with an allergy to tixocortol pivalate were not detected with this mix (75), presumably due to masking by the anti-inflammatory effect of the other constituents. This method cannot therefore replace testing with individual markers. A series of specialized 'CS' tests is needed to detect possible cross-reactions and determine potential replacement agent(s).

The vehicle. While petrolatum works well for tixocortol pivalate and budesonide, for most CSs, ethanol is the first choice of vehicle (76, 77). Because of its weak trans-epidermic penetration, hydrocortisone is an exception to this rule and optimally requires for its preparation an equal mixture of ethanol and dimethyl sulfoxide (76).

Although CSs are unstable in ethanol and may degrade after just 1 month of storage in a refrigerator, several studies have shown that skin tests carried out with fresh and preserved solutions give comparable results (78). This might relate to the fact that the actual allergen is often a degradation product of the agent rather than the CS itself, therefore instability in the solution does not affect

the sensitivity of the test. Isaksson et al. (78) suggested preparing new solutions every 6 weeks to avoid false negatives.

Concentration. As a result of the anti-inflammatory activity of CSs, weakly sensitized patients exhibit an inverse relation between the concentration of the test solution and the rate of positive responses. If the concentration is too low, false negatives can result unless the test is applied to eczematous skin. If the concentration is too high, then the anti-inflammatory effect dominates and again a false negative can result. Furthermore, there is a small risk that skin tests may sensitize the patient (79). However, higher concentrations are sometimes necessary when there are negative test results (at the usual concentrations) and a strong clinical suspicion of allergy. Numerous publications have debated the optimal test concentration of CS in test preparations.

Comparative studies have shown that the 0.01% budesonide and 0.1% tixocortol pivalate tests will detect most patients allergic to CSs (73, 80). According to studies carried out by Isaksson et al. (71, 81, 82),

however, in some cases, still weaker solutions (between 0.02% and 0.002%) are necessary to diagnose patients with budesonide allergy. Most other CSs are tested at a concentration of 1%, as for hydrocortisone 17-butyrate (72).

The reading. The anti-inflammatory effect of a CS also influences the reading time. Especially when the concentration is high, the reaction may be falsely negative at early readings, because the anti-inflammatory effect can mask the allergic reaction. For this reason, numerous authors have proposed readings on day 6 or day 7, or even later (17, 83).

Particular effects related to CSs are:

- 'Edge effect'

The anti-inflammatory properties of CSs also lead to the so-called 'edge effect' (a ring of induration, erythema, and/or papulovesicles around the patch test site, with no reaction in the centre) which usually appears on early readings (36). This phenomenon can be explained by a higher concentration of allergen in the centre of the patch, where there is therefore a more powerful anti-inflammatory effect; this is in contrast to the edges where there is diffusion of the CS, resulting in a lower concentration. This phenomenon tends to disappear in later readings, when the site of the patch test becomes entirely eczematous (Fig. 2, edge effect).

- Vasoconstriction and vasodilation

Other problems frequently encountered in skin testing are an initial period of vasoconstriction, resulting in whitening of the skin (and the attendant risk of a false-negative) and so-called 'skin blanching', followed by massive vasodilation with marked erythema (and the attendant risk of false positive) (36).

Additional tests. Repeated open application tests can also be useful and are sometimes the only way to achieve a diagnosis (84). Some authors have also proposed that in suspected cases, negative patch tests should be completed by IDR with late readings (85, 86). Intradermal reaction tests eliminate the possibility that only limited penetration of the allergen is achieved. However, it is possible that *contact* between the CS and epidermal cells, as well as metabolism in the latter, play an important role in the allergenic process. Finally, they involve a number of secondary effects: pain at the injection point, local skin atrophy, and an increased risk of active sensitization (87).

Last but not least, it is also important to test other active principles, the vehicle, and preservatives present in the preparations used. The allergens most often associated with topical CSs are neomycin, propylene glycol, wool alcohols, benzyl alcohol, and sorbic acid (18, 88). Allergy to additives, such as sodium carboxymethylcellulose (89, 90), which is a semi-synthetic hydrosoluble



Figure 2. Edge effect.

polymer with high molecular weight that is used as an excipient in numerous injectable CS preparations (especially intra-articular solutions), should also be ruled out.

Immediate AHS. Immediate allergic reactions can be detected by prick tests (at concentration of 1 mg/ml) and early IDR readings (30 min). If the prick test is negative, then intradermal tests at progressively higher concentrations (1/1000, then 1/100 of the prick solution) are carried out, and for which the lowest nonirritant concentration needs to be defined. Later readings will allow the detection of semi-delayed reactions (Fig. 3, intradermal testing, example of positive result for methylprednisolone and hydrocortisone).

The aforementioned paradoxical action of cutaneous tests for delayed allergies (i.e. the competition between allergic reaction and anti-inflammatory effect) does not seem to occur in immediate skin tests. As mentioned by Nancey et al. (91), CSs are able neither to prevent nor improve experimental urticaria, i.e. wheal and flare, and they even enhance histamine and codeine-induced erythema.

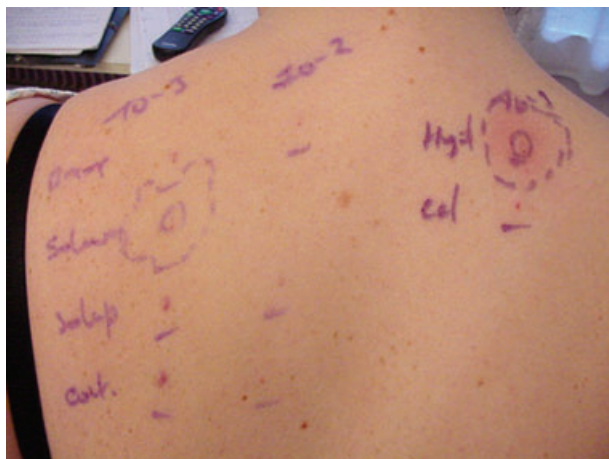


Figure 3. Intradermal testing, example of positive result for methylprednisolone and hydrocortisone.

Additional measures to diagnose reactions to systemic CSs

The initial investigation. When confronted with a patient with a reaction to systemic administration of a CS, the diagnostic approach must also be rigorous. It is important to know the nature of the symptoms and their chronology (prior contacts, the time interval between the appearance of symptoms and the last drug administration, the effect of stopping the treatment), to be aware of other drugs the patient might have been taking when the reaction occurred, and to know the history (prior allergic reactions, family history of drug allergies).

Reintroduction tests (DPT: drug provocation testing). If the skin tests turn out to be negative, reintroduction tests must be carried out with the CS and its vehicles, including the preservative agents. Oral provocation tests remain the gold standard for confirming or refuting the patient's hypersensitivity to a given substance, as they reproduce clinical symptoms regardless of the underlying aetiological or pathogenic mechanism (92). However, such a test should be carried out only when less dangerous diagnostic procedures have failed to give conclusive results.

In vitro tests

Skin tests carry the risk of inducing an allergic reaction that is similar to the original incident, as well as the risk of sensitizing the subject, and may sometimes not be conclusive. *In vitro* tests therefore have valuable advantages.

Delayed allergic hypersensitivity

Biological tests for DH are designed to demonstrate that a drug activates specific T-cells. So far, only LTTs have been described for CSs (3, 93–95), whereas techniques

such as ELISPOT for IFN- γ , which measures the secretion of cytokines after *in vitro* (re)stimulation by a drug (this technique has been used particularly for β -lactam antibiotics), are potentially promising.

Lymphocyte transformation test. This is the most common method of detecting sensitization to drugs. Lymphocyte transformation test measures the proliferation of lymphocytes exposed *in vitro* to the drug. The sensitivity of this test is usually about 60–70%, but this number is highly dependent on the specific antigen (drug) tested.

In addition, according to some authors (96, 97), the proliferation response can only be induced in the presence of dendritic cells as antigen-presenting cells, which play a fundamental role in skin sensitization to CSs. Lauerma et al. (97) examined the capacity of CSs to induce *in vitro* proliferation of T lymphocytes from patients with allergic contact dermatitis to CSs. With peripheral blood mononuclear adherent cells as antigen-presenting cells and hydrocortisone-17-butyrate as hapten, no proliferation responses were detected. However, when epidermal Langerhans cells were used as antigen-presenting cells, weak proliferation responses were observed.

Enzyme-linked immunospot gamma-interferon assay. Gamma-interferon, a Type 1 cytokine expressed by activated T-cells, seems to play an important role in the physiopathology of drug DH reactions. Enzyme-linked immunospot gamma-interferon assay is a fast, sensitive and reproducible technique for analysing the presence and number of cytokine-producing, antigen-specific T-cells. The sensitivity and specificity of this technique were recently evaluated at 91% and 95%, respectively, for diagnosing delayed hypersensitivity to β -lactam antibiotics (12). Ongoing studies should determine whether this extends to other drugs including CSs, as well as whether it will be possible to validate this technique as a diagnostic tool for use in routine clinical practice.

Immediate hypersensitivity

Specific IgE. Only a few authors have been able to demonstrate the presence of specific IgE antibodies in patients with an immediate reaction to CSs by using immunoblotting technique (54, 63–65), presumably due to the hapten' nature of CSs.

Basophil activation test. The basophil activation test, based on flow cytometry, consists of analysing and quantifying changes in the expression of blood basophil activation markers in the presence of a given allergen (10, 11, 98). The most common activation markers are CD63 and CD203c. This technique has been validated for a variety of IgE-based airborne and food allergies, as well as for allergies to latex, hymenoptera venom, and certain drugs (myorelaxants, β -lactam antibiotics) (10).

Encouraging results have also been obtained for CSs (D. Ebo and A. Rozières, unpublished data).

Classification, allergenicity and cross-reactivity

Most of the studies on the allergenic nature and cross-reactions among CS that will be discussed here, concern topical CS. Whether similar reactive profiles apply to CS administered via the systemic or oral routes remains to be demonstrated.

Chemical structure

The structure of steroid hormones is based on a cyclopentanoperhydrophenanthrene nucleus: three rings of six carbon atoms and one ring of five carbon atoms (99). Steroids synthesized by the adrenal cortex contain 19 or 21 carbon atoms. Some molecules of the latter group have a hydroxyl group attached to the 17th carbon atom, and are called 17-hydroxycorticosteroids. The activity of these steroids is predominantly gluco-mineralo-corticoid. Cortisol, or hydrocortisone, is the principle steroid of this group (Fig. 4, chemical structure of hydrocortisone with the conventional numbering of carbon atoms).

In order to fully exploit the therapeutic properties of natural glucocorticoids, the pharmaceutical industry has developed a huge number of variants through minor chemical and structural changes. The objectives of this research are to obtain better cutaneous penetration, slower enzymatic degradation, and a greater affinity for the cytosolic receptors.

The principal structural changes are:

- Creating a double bond between C1 and C2 (to obtain prednisolone).
- Halogenation (substituting a fluorine or chlorine atom, usually in position C6 and/or C9).
- Introducing a methyl group at C16, hydroxyl groups at C16 and C17, or an acetonide bond between C16 and C17.

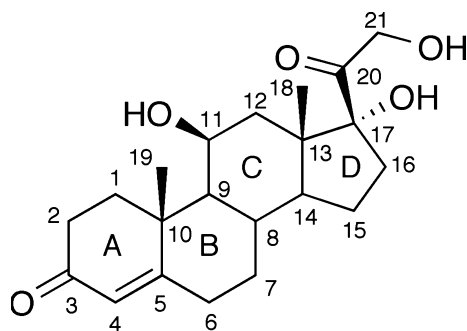


Figure 4. Chemical structure of hydrocortisone with the conventional numbering of carbon atoms.

- Esterification of C17 and/or C21, which makes the molecule more lipophilic and increases its ability to penetrate the skin.

The more powerful the CS are, the more significant are their side-effects. Thus, in addition to the objectives listed earlier, pharmaceutical research has made efforts to dissociate useful traits from undesirable effects. The addition of an ester function, e.g. increases lipophilicity and therefore skin penetration. At the same time, the rapid hydrolysis of ester creates a steep gradient in the CS concentration with respect to deeper skin layers. This description applies to a number of CSs with labile esters, such as prednicarbate and methylprednisolone aceponate. On the contrary, these molecules seem to have non-negligible allergenic properties.

The pharmaceutical industry thus has to meet a new challenge: to develop agents that are not only powerful and well tolerated (i.e. with the lowest possible 'classical' side-effects), but also with weak allergenic properties. With respect to injectable agents, the solubility of derivatives in an aqueous or saline solution is often improved by coupling an ester group to C21; this is also the case for succinate esters, which are particularly likely to trigger an allergic reaction because of this characteristic.

The allergenic capacity of CSs

The development of an allergic reaction depends on the degree of immunogenicity of each drug: not only an agent's chemical structure and configuration, but also its ability to penetrate skin and the degree of exposure to immunocompetent skin cells play an important role. Besides the drug itself, there are the factors associated with individual characteristics, i.e. the immune system's ability to identify the antigen, the enzymatic repertoire and activity giving rise to metabolites for a given drug (which vary both in type and quantity) that may exert a different sensitizing capacity, as well as genetic predisposition; e.g. as proposed by Wilkinson et al. (25), hydrocortisone allergy seems to be associated with the HLA DR8 genotype while negatively associated with HLA DR3. Moreover, there may be infectious co-factors involved.

Skin penetration and exposure to immunocompetent cells. Several factors influence the degree of skin penetration, and therefore the risk of sensitization: the vehicle used, the CS concentration, the lipophilicity of the agent, the application mode, the frequency of application, the area treated, as well as the age of the patient and the condition of the skin surface being treated. Some CSs are capable of forming a reservoir in the keratinous layer, which gradually releases the drug and lengthens the exposure to immune cells.

Skin occlusion, which increases the pH as well as the skin penetration, therefore also increases the risk of sensitization. This explains the high frequency of CS hypersensitivity in patients with stasis dermatitis, venous ulcers, or anogenital dermatitis conditions that are characterized by maceration.

Skin metabolism routes. The process of skin metabolism plays an important role in the allergenic potential of CSs and also influences their cross-reaction profiles (24). The cutaneous metabolic reactions involved in the biotransformation of CSs have not yet been fully determined. The epidermis is a metabolically-active structure containing a variety of enzymes, in this respect acting much like other organs (the liver, for instance). One of the most important steps in metabolizing CSs is hydrolysis. Indeed, for some agents, chemical or enzymatic hydrolysis of the ester function is often necessary to obtain sufficient biological activity (100). The role of hydrolysis depends on the stability and size of the ester, the conditions under which the product was preserved, and the patient's enzymes. C21 esters are less stable (labile) and thus easily hydrolyzed, whereas C17 esters are much more resistant. Agents with both a C17 mono-ester function and a C21 hydroxyl group, however, are also unstable in an acidic or alkaline environment, and after hydrolysis of the C21 ester, the C17 ester can rapidly undergo nonenzymatic conversion into the C21 mono-ester. Enzymatic hydrolysis then quickly follows, converting it into free alcohol. In general, CSs which metabolize rapidly in the skin (the D2 group of labile esters) produce allergic reactions more often than those that metabolize slowly or not at all.

Sensitization capacity of metabolites. It has become clear that the allergen that triggers an immune reaction may not be the CS itself but may be a by-product of its metabolism. The principal metabolites of hydrocortisone in an aqueous or alcoholic solution are dehydro-21 of steroid glyoxals (101). Not all agents have the same sensitization capacity, which explains the large differences observed between various CSs.

Protein binding

Steroid glyoxals and protein binding. Assuming that all CSs interact with proteins in the same manner, it would be steroid glyoxals or 21-dehydrocorticosteroids (aldehydes) that would bind to nucleophilic protein residues (101, 102). Both types are metabolites or products of CS degradation, either oxidative or otherwise. Oxidation of the C21-hydroxyl function creates two derivatives: 21-dehydro and the very reactive α -cetoaldehyde. Tests carried out by Matura et al. on CSs and their corresponding aldehydes support the hypothesis that these metabolites or degradation products play a role in sensitization (103). In addition, subjects allergic to CSs

are more often sensitized to ethanol, which is also metabolized by dehydrogenase into an aldehyde. If the subject suffers from an enzyme dysfunction (because of chronic hepatitis or genetic factors, for example), then reaction of these two types of molecules can result in accumulation of aldehydes (103–105) (Fig. 5, positive skin tests to aldehydes and ethanol).

After binding to guanidine (a residue of arginine), the molecules generated by CS degradation create stable immune complexes which are responsible for delayed hypersensitivity (24, 101). It has been shown that steroid glyoxals can bind to every amino acid except proline and hydroxyproline. The arginine reaction, however, is clearly predominant – and also irreversible (106, 107). Wilkinson et al. (106) showed that CSs with a greater capacity to bind to arginine do have stronger allergenic properties and recently, Berl et al. (107) confirmed that steroids selectively react with arginine to form important adducts.

Other protein-binding mechanisms have been described (106). In thioesters such as tixocortol pivalate, which has a thioester group at C21, hydrolysis produces tixocortol which binds rapidly to amino acids such as methionine via a disulphur bridge.

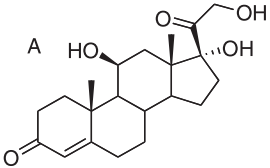
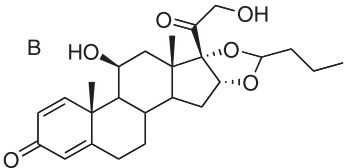
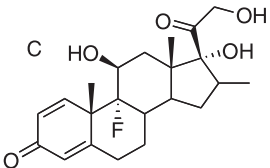
Halogen substitution. Corticosteroids without fluorine substitution experience more rapid metabolic degradation, and therefore bind more easily to arginine than their fluorinated derivatives, hence, are more likely to induce allergic reactions.

Methyl substitution at C16 and/or ester substitution at C17. The presence of a methyl group at C16 and/or a long ester chain at C17 seems to protect the molecule from rapid degradation (102), hence, it produces still fewer allergic molecules.



Figure 5. Positive skin tests to aldehydes and ethanol.

Table 2. Classification of CSs

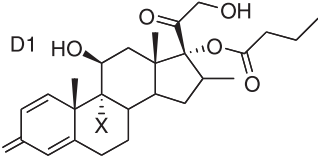
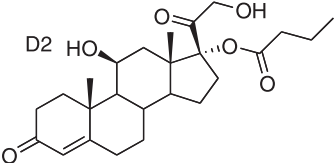
Group	Characteristics of the group	Typical members	Possible cross-reactions outside the group
 A	No substitution on the D ring except a short chain ester or a thioester on C21	Tixocortol pivalate Cloprednol Cortisone acetate Hydrocortisone Hydrocortisone acetate Hydrocortisone 21-butyrate Hydrocortisone hemisuccinate Mazipredone Medrysone Methylprednisolone acetate Methylprednisolone hemisuccinate Prednisolone Prednisolone metasulpho benzoate Prednisolone succinate Prednisolone pivalate Prednisolone caproate Prednisone Dichlorisone acetate Fludrocortisone acetate Fluormetholone Fluprednisolone acetate Isofluprednone acetate	D2
 B	C16, C17 cis Ketal or diol structure, possibly a side chain on C21	Budesonide Amcinonide Desonide Fluchloronide Flumoxonide Flunisolide Fluocinolone acetonide Halcinonide Triamcinolone Triamcinolone diacetate Triamcinolone hexacetonide Fluocinonide Triamcinolone benetonide Triamcinolone acetonide	
 C	C16 methyl substitution on the D ring, no side chain on C17, possibly a side chain on C21	Betamethasone Betamethasone Na-phosphate Desoxymethasone Dexamethasone Dexamethasone acetate Dexamethasone Na-phosphate Diflucortolone valerate Flumetasone pivalate Flucortin butyl Flucortolone Flucortolone caprylate Flucortolone pivalate Fluprednidene acetate Halomethasone Meprednisone	

Cross vs concomitant reactions

Sensitized patients often test positive to several CSs. Although the existence of cross-reaction phenomena has been proved, e.g. obtaining positive skin tests for synthetic CSs to which a patient could *never* have been

exposed (because they are not yet on the market), simultaneous or subsequent sensitizations can never be entirely ruled out. It is often extremely difficult to determine as to which CS a patient has been exposed to in the past. As Issakson emphasized, it is therefore more appropriate to mention *concomitant sensitization* (which

Table 2. (Continued)

Group	Characteristics of the group	Typical members	Possible cross-reactions outside the group
 D1	Methyl substitution on C16, halogen substitution, side chain ester on C17, possibly a side chain on C21	Beclomethasone dipropionate Betamethasone dipropionate Betamethasone 17-valerate Clobetasol propionate Clobetasone butyrate Diflorasone diacetate Mometasone furoate Fluticasone propionate Alclomethasone dipropionate	
 D2	No methyl substitution on C16, no halogen substitution, side chain ester on C17, possibly a side chain on C21	Hydrocortisone 17-butyrate Hydrocortisone aceponate Methylprednisolone aceponate Prednicarbate Difluprednate	A Budesonide (S isomer)

may include cross-reactions) (108). For this reason, the possibility of using animal models has been studied (109, 110). Beside patch test data, statistical and three-dimensional structural analysis can also address the cross-reactivity issue.

Cross-reactions: ABCD classification. In 1989, based on structural and clinical characteristics, Coopman et al. (111) classified CSs into four reactivity groups, namely Groups A, B, C and D, the volume occupied by substituents on the D ring of the CS molecule being a critical element of CS binding to skin proteins.

In 1995, Lepoittevin et al. (112) carried out conformational analysis of the observed cross-reactivities between CSs, which supported this classification. Groups A, B and D are indeed very homogenous in terms of molecular structure and significant differences are only evident between CSs of different groups. The behaviour of budesonide, which cross-reacts not only with other acetonides but also with CS esters, can be attributed to its unique molecular structure: an acetal function gives it a resemblance to molecules from both Groups B and D, respectively, according to their stereospecificity. Group C, despite its structural similarity to Group A, has no unifying characteristics in terms of structure or volume.

Further clinical data led Matura and Goossens (24, 100) in 2000 to confirm the existence of the four CS groups (the ABCD classification). However, the behaviour exhibited by certain constituents of Group D led them to propose a further subdivision into two subgroups i.e. D1 and D2. Molecules in Group D1 carry a methyl group in C16 and have a halogen atom in the B ring, whereas molecules in Group D2 have neither substitution.

Moreover, D2 CS have an instable ester function with lipophilic properties (enhancing skin penetration), which are rapidly metabolized in the skin (cf supra).

The five groups are given in Table 2.

The CSs in Groups C and D1 have provoked very few allergic reactions and usually do not interact with CSs from the other groups. In mometasone furoate, e.g. the specific configuration of the C17 lateral chain explains the low number of positive skin reactions observed (113). Fluticasone propionate possesses not only a fluorine atom at C9 but also a methyl substitution at C16 and a unique structure at C17 that prevents the hapten-protein bond from forming. The risk of primary sensitization to this CS is extremely low, and its cross-reactions with other CSs are weak (114).

The CSs in Group D2, on the contrary, along with those in Group A and also budesonide, produce allergy more frequently. These agents often cross-react, both within the same group, and with agents belonging to other groups.

Intra-group cross-reactions. Cross-reaction between CSs of the same group can usually be explained in terms of structural similarities or a shared metabolic pathway. Several studies have shown that the allergenic epitope responsible for CS recognition is always found on or near the D ring. As previously described, the molecular structure of the D ring is homogenous within a group. Because the metabolization pathways of different agents in the same group are often identical or very similar, the haptenic structures formed by their metabolites cannot always be distinguished by the lymphocyte clone(s) responsible for the allergic reaction.

Inter-group cross-reactions. There are undisputed cases of cross-reaction between agents of different groups.

Groups A and D2. The CSs of Group D2 are rapidly transformed in the skin, becoming analogues with free C21 and/or C17 hydroxyls. Thus, while the agent applied

to the skin is one of the 'labile ester' CSs (D2), its metabolite corresponds more closely to Group A. One example of intracutaneous biometabolization is the conversion of hydrocortisone 17-butyrate (Group D2) to hydrocortisone (Group A). This illustrates the typical cross-reaction observed between Groups A and D2.

Budesonide and Group D2. Budesonide can be considered as a unique case in the following sense: its acetal function is actually an equal mixture of the R and S diastereoisomers (112). Both R and S diastereoisomers can develop cross-reactions with Group B CSs, but only the S diastereoisomer can cross-react with Group D2 CSs (115). An analysis of their configuration shows that while the R isomer exhibits symmetry that is characteristic of the B group, the S isomer can take on an asymmetric aspect. The result is a large hydrophobic 'cavity' at the C17 ester function, similar to Group D agents.

Sex-hormonal steroids. It has been observed that some patients sensitized to CSs respond positively to skin tests with other steroids, such as the sex-hormonal steroids (116, 117). Wilkinson and Beck (118) estimated the prevalence of 17-hydroxyprogesterone allergies in patients reacting positively to hydrocortisone to be 19–26% and considered these to be the expression of cross-sensitivity. They also considered that in most cases there are no clinical consequences. However, CS allergy can induce an allergy to, e.g. endogenous progesterone, for which the clinical presentation is a generalized eczematous eruption that gets worse during the premenstrual period: so-called auto-immune progesterone dermatitis (AIPD) (119). On the contrary, any patient presenting symptoms compatible with AIPD should also be tested for CS allergy.

Other hypotheses regarding cross-reactivity. The ABCD classification cannot explain all observed cross-reactions. Furthermore, a purely structural analysis of CSs does not justify the existence of Group C.

Wilkinson et al. suggested that each CS has several immunological sites (120) and consider that there are two principal sites involved in immune recognition, i.e. the C16/C17 and C6/C9 substitutions. They emphasized that modifications to the C21 lateral chain do not influence the allergenic nature of the substance, probably due to skin metabolism and degradation of these esters. They also (120, 121) claimed that B-ring halogen substitutions (C6 or C9) are the major determinants of cross-reactions between CSs. Although the fluorine atom is similar in shape and size to the hydrogen atom, they explain the different reactivity of halogenated and non-halogenated molecules as being caused by charge differences (122). Hydrogen is relatively electro-positive and

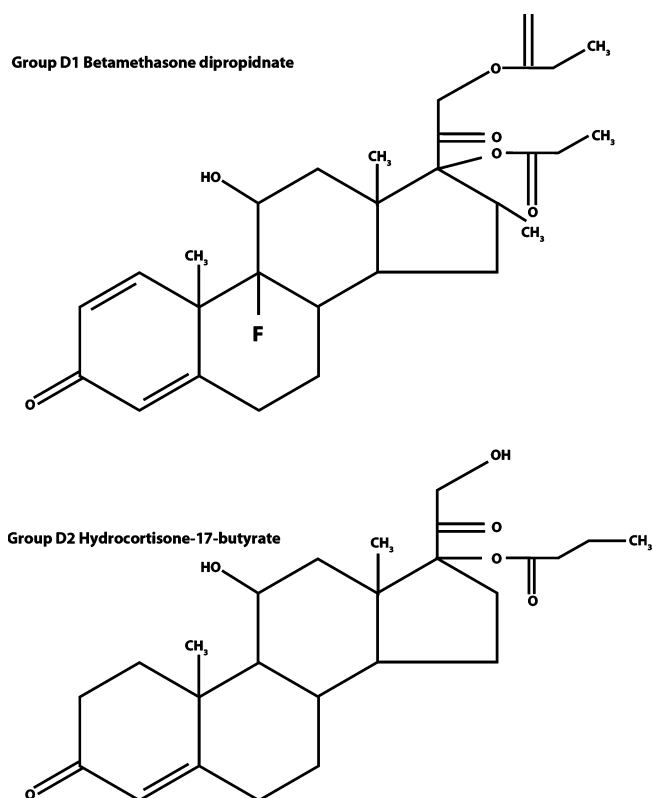


Figure 6. Groups D1 and D2: structural characteristics.

fluorine is electro-negative. It is also possible for a halogen atom in position C9 to exert an electrical attraction on the carbon atom at C11, conferring a higher stability to the CS and therefore limiting the creation of allergenic by-products. Several authors have based their work on Wilkinson's hypothesis, proposing halogenated replacement agents for their allergic patients. However, while this rule (positive allergic responses are less frequent for fluorinated derivatives) seems to hold in Groups A, C and D1, there seems to be no difference between fluorinated and nonfluorinated derivatives in Group B.

The respective role of methyl and halogen substitutions remains unclear when determining a CS's capacity to induce allergy. The significant difference between CSs in Groups D1 (with a methyl group at C16 and a B-ring halogen) and D2 (with neither substitution) is taken to illustrate this observation (Fig. 6, structural characteristics).

A few patients develop hypersensitivity to almost the entire spectrum of synthetic CSs (Fig. 7, positive skin tests to multiple CSs). One hypothesis is that these individuals possess a powerful enzymatic hydrolysis system that transforms all steroids into hydrocortisone or similar agents to which they are sensitized (34). They may also develop T lymphocytes that recognize the basic structure of the CS (123) or common structures within the various groups (111). Indeed, it is often difficult to classify



Figure 7. Positive skin tests to multiple CSs.

CSs with short ester chains or agents that combine several substitutions.

While this review points to other subtle but important features of CSs that are relevant to their allergenic potential, and despite some inconsistent results and unanswered questions, the ABCD classification and D1, D2 subclassification have many important clinical implications and all practitioners should be aware of the group to which a prescribed CS belongs.

Specific characteristics of the systemic route

Patients sensitized to a systemically administered CS also often exhibit positive tests to other CSs. It needs to be determined whether concomitant reactions observed in these cases relate to the same classification.

Immediate reactions

Pathogenesis. The pathogenesis of immediate CS reactions is still poorly understood.

Allergic hypersensitivity. Only a few authors have found evidence for IgE antibodies that are specific to certain CSs (54, 63–65). However, neither negative test results nor the absence of specific IgEs rule out the possibility of a reaction as a result of specific antibodies.

Nonallergic hypersensitivity. Pseudo-allergic reactions or idiosyncrasies similar to those observed with acetylsalicylic acid (including overproduction of leukotrienes by blocking of the cyclooxygenase pathway) could explain certain immediate CS reactions (20, 124). Other IgE-independent mechanisms involve the release of histamine by mast cells. Acute cardiovascular toxic reactions have also been described in patients who receive high and rapidly infused doses of CSs (22, 125). These

reactions seem to be due to an α -adrenergic blockage and the drug's negative inotropic effect, rather than to an immunological phenomenon.

Cross-reactions. Few authors have studied the possibility of extending the classification described by Coopman et al. (111) to immediate reactions. The most frequently implicated CSs are hydrocortisone and methylprednisolone, which belong to Group A according to the ABCD classification, within which cross-reactions may be observed (32). Venturini et al. (126) reporting on seven cases of immediate hypersensitivity to systemic CSs could not demonstrate the existence of cross-reactions between CSs belonging to the same group. Similarly, some patients who are allergic to hydrocortisone and methylprednisolone (esterified or not), do tolerate prednisolone and/or prednisone, and all these drugs belong to the Group A (32, 127–129).

Burgdorff et al. (63) described the case of a patient with allergy to methylprednisolone sodium succinate, who presented cross-reactions with all agents carrying the same succinate ester. Skin tests and the reintroduction of other CSs without this particular ester or with another C21 substitution were all negative without exception. Others have confirmed the absence of cross-reactions between succinate CSs and agents carrying other esters (phosphate, for example), or with nonesterified hydrocortisone or methylprednisolone (66, 67, 89, 130–132). The opposite may also occur; e.g. reactions to native hydrocortisone and methylprednisolone, but not to their corresponding sodium succinate salts (133).

A high tolerance to halogenated betamethasone and dexamethasone CSs in patients who are allergic to hydrocortisone and methylprednisolone was found in several studies (128, 129, 134–136). With regard to immediate allergic reactions, two authors failed to detect any cross-reactivity between betamethasone and dexamethasone (agents with identical chemical structure, differing only in the position of the C16 methyl group) (137, 138).

Thus, immediate hypersensitivity to CSs would seem to be a rather heterogeneous phenomenon. Certain patients react to the steroid itself, others to a specific esterified derivative. It appears that, in contrast to other esters such as phosphates, the succinate esters of hydrocortisone and methylprednisolone are frequently involved in immediate hypersensitivity reactions, the mechanism of which is unclear. Moreover, halogenated derivatives are rarely implicated.

Delayed reactions

It is extremely difficult to analyse the cases of delayed reactions to systemic CSs published in the literature, as a result of differences in the nomenclature used to describe these observations and to the lack of standardization of diagnostic methods.

Conclusion

Allergic hypersensitivity to CSs is a common finding in a dermatological practice, the skin being the main sensitization route, and delayed-type allergic reactions are much more frequently encountered than immediate-type reactions. As a result of the anti-inflammatory properties of CSs, however, the clinical signs of allergy may be masked and the results of skin tests difficult to interpret. Hence, CS allergy still remains unfamiliar to many clinicians who often prescribe these drugs, both for topical or systemic administration.

Moreover, because of the frequent occurrence of cross-reactions between these agents, CS-allergic patients, even when recognized as such, are sometimes still prescribed a CS that they cannot tolerate.

With regard to the cross-sensitivity patterns, the ABCD classification and D1, D2 subclassification seem very useful in directing the search for a replacement

agent, but cannot be a substitute for a systematic, individualized evaluation of each patient's sensitization/tolerance profile. Further studies are still needed to validate this classification of allergic contact dermatitis and to determine whether this classification is also useful for immediate and delayed reactions to systemic CSs.

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