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# Immediate and delayed hypersensitivity reactions to corticosteroids – prevalence, diagnosis and treatment

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## Summary

BACKGROUND: Corticosteroids, which are anti-inflammatory and immunosuppressive agents used for the treatment of various diseases including allergic disorders, can induce immediate and delayed hypersensitivity reactions. Although these reactions are not common, due to the wide usage of corticosteroid medications, corticosteroid hypersensitivity reactions are clinically important.

OBJECTIVE: In this review, we summarise the prevalence, pathogenetic mechanism, clinical manifestations, risk factors, diagnostic and therapeutic approach for corticosteroid-induced hypersensitivity reactions.

METHODS: An integrative review of the literature was conducted using PubMed searches (mainly large cohort-based studies) regarding the different aspects of corticosteroid hypersensitivity.

RESULTS: Hypersensitivity reactions to corticosteroids can be immediate or delayed and can follow all modes of corticosteroid administration. Prick and intradermal skin tests are useful diagnostic tools for immediate hypersensitivity reactions, patch tests are useful for delayed hypersensitivity reactions. According to the diagnostic tests an alternative (safe) corticosteroid agent should be administered.

CONCLUSION: Physicians of all medical disciplines should be aware that corticosteroids can cause ("paradoxically") immediate or delayed allergic hypersensitivity reactions. The diagnosis of such allergic reactions is challenging since it is often difficult to distinguish between hypersensitivity reactions and deterioration of the basic inflammatory disease (e.g., worsening of asthma or dermatitis). Thus, a high index of suspicion is needed in order to identify the culprit corticosteroid.

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## Introduction

Corticosteroids have been widely used for many years for the treatment of various diseases such as asthma, allergic disorders, autoimmune disorders, after transplantation (solid organ as well as bone marrow / stem cell transplantations), nephrological and dermatological disorders, owing to their anti-inflammatory effects and immunosuppressive properties [1, 2]. Corticosteroids can be administered via different routes: orally, intravenously, intraarticular, intramuscularly, sub-cutaneously, topically (drops/creams) and by inhalation (nose/lungs) [1, 2]. As discussed below, corticosteroid agents can be classified into several classes according to their chemical compositions [3–5].

In spite of their beneficial effects, corticosteroids can cause significant adverse effects such as immunosuppression, hypertension, diabetes, osteoporosis, avascular necrosis and growth retardation in children [6]. Although corticosteroids are commonly used for the treatment of various allergic disorders [7], they may cause, though quite uncommonly, allergic hypersensitivity reactions. Because of the wide usage of corticosteroids, even uncommon allergic hypersensitivity reactions are clinically important, thus physicians (general practitioners as well as allergy and dermatology specialists) should be aware of such reactions. The allergic hypersensitivity reactions can be immediate (usually up to 1 hour after corticosteroid administration) or delayed (appearing after more than 1 hour up to several days after corticosteroid administration) [8–12]. Klim Gittelman et al. and Borja et al. reported immediate hypersensitivity reactions in 0.1–0.3% of patients under systemic corticosteroid treatment [13, 14]. However, the real prevalence of such reactions is unknown since large control studies are not available and most of the relevant data are based on case reports. Delayed hypersensitivity reactions, which are more common than immediate reactions, were reported in 0.5–5% of patients under corticosteroid treatment (especially topical) [6, 15].

Several risk factors have been reported to be associated with both immediate and delayed corticosteroids allergic hypersensitivity. Cutaneous alkalisation (e.g., in sweat areas, skin infections, atopic dermatitis, venous stasis) may lead to a high cortisol degradation rate with high arginine binding, which increases cortisol antigenicity [8, 16]. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) and prolonged treatment with high-dose corticosteroids were also reported to be risk factors for corticosteroid hypersensitivity reactions [12, 17–19]. Immediate allergic hypersensitivity reactions to corticosteroids are mediated, at least in part, by specific Ig-E antibodies (type I response). However, non-IgE-mediated immediate aller-

gic reactions involving direct activation of mast cell, basophils or the complement system, as well as inhibition of the cyclooxygenase pathways, were also reported in the pathogenesis of immediate corticosteroids hypersensitivity reactions [8, 12, 18]. Delayed allergic hypersensitivity reactions to corticosteroids are mostly mediated by T cells (type IV response) [8, 19]. It appears that binding of the corticosteroids (or their degradations products) to cutaneous or serum proteins generate stable antigens (allergens), which stimulate the immune system towards an allergic (type I immediate and type IV delayed hypersensitivity reactions) response [8, 9]. As discussed below, the allergic response may be directed not only against the culprit corticosteroid agent, but also against other corticosteroids of the same class, although cross-reactivity between different corticosteroid classes was also reported (see table 1) [4–6]. Class cross-reactivity (for allergic hypersensitivity reactions) was mainly reported for patients with delayed hypersensitivity reactions to corticosteroids, whereas such cross-reactivity for patients with immediate reactions is not yet established [11, 12, 18, 20, 21].

**Table 1:**
Classes of corticosteroid medications [4, 5, 8, 9].

| |
|---|
| **Class A** |
| Hydrocortisone |
| Prednisone |
| Prednisolone |
| Methylprednisolone |
| Cortisone acetate |
| Fludrocortisone |
| Tixocortol pivalate*/** |
| **Class B** |
| Triamcinolone acetonide |
| Fluocinolone acetonide |
| Desonide |
| Fluocinonide |
| Halcinonide |
| Flunisolide |
| Budesonide*/** |
| **Class C** |
| Betamethasone* |
| Dexamethasone |
| Fluocortolone |
| Desoximetasone |
| Paramethasone |
| **Class D1** |
| Beclomethasone* |
| Beclomethasone dipropionate |
| Beclomethasone valerate |
| Betamethasone dipropionate |
| Betamethasone valerate |
| Clobetasol-17-proprionate |
| Clobetasone-17-butyrate |
| Mometasone furoate |
| Fluticasone |
| **Class D2** |
| Methylprednisolone aceponate* |
| Prednicarbate |
| Difluprednate |
| Hydrocortisone-17-butyrate |
| Hydrocortisone-17-propionate |

* Preferred agents (from each class) for patch test

** Included in the ESCD (European Society of Contact Dermatitis) recommended standard for patch test [46]

Glucocorticoids are classified according to chemical structure and side chains. Delayed hypersensitivity to one class member usually indicates cross reactivity to all class members. Data regarding cross reactivity between class members in immediate type hypersensitivity is not yet established.

## Classes of corticosteroid medications

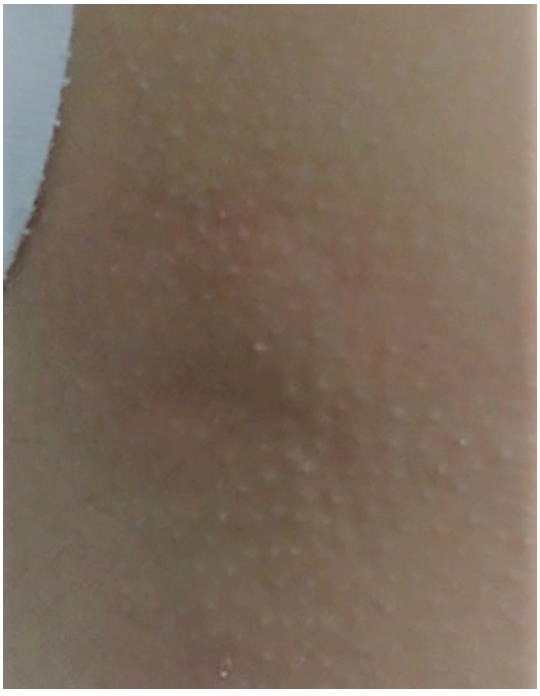
Corticosteroid agents are divided into five classes according to their chemical characteristics (e.g., side chains, hydrogenations, methylations) (table 1) [4–6]. This classification is important for the evaluation and management of hypersensitivity allergic reactions (mainly delayed type).

Class C and D1 cause very few allergic reactions. Most allergic reactions were observed following treatment with class A (mainly hydrocortisone, methylprednisolone and prednisone) corticosteroid agents followed by class B (mainly triamcinolone) and class D2 corticosteroids (table 1). Because of cross-reactivity with co-sensitisation between agents of the same class, corticosteroid allergic hypersensitivity is usually not drug specific. D2 corticosteroids also share co-sensitivity with classes A and B [5, 22]. Recently, Beack et al. suggested a new classification with division into three classes of corticosteroids. Class 1 includes classes A and D2, class 2 includes class B and class 3 includes classes C and D1 [23]. Because of the chemical similarities within corticosteroids classes (table 1), allergic reactions to one class member may occur following treatment with another member of the same class. Thus, an agent of different corticosteroid class should be considered as an alternative agent.

## Immediate allergic hypersensitivity reactions

Immediate allergic hypersensitivity reactions (presenting usually within 1 hour of corticosteroid administration)

**Figure 1:** Urticarial rash typical of an immediate hypersensitivity reaction few minutes after intravenous administration of hydrocortisone 50 mg.



have been reported with almost all corticosteroid agents [11] and following all routes of administration (oral, intravenous, intramuscular, subcutaneous, intra-articular, inhalation, nasal and topical) [18, 24]. The most prevalent culprit agents are hydrocortisone, prednisone, methylprednisolone and triamcinolone acetate (class A agents) [20, 25–29]. Immediate allergic hypersensitivity reactions include anaphylaxis, urticaria, angioedema, flushing and presyncope (fig. 1) [8, 11, 20, 24]. Baker et al. reported that the most common routes of corticosteroid administration causing immediate allergic reactions were intraarticular followed by oral and intravenous treatment [20]. Other reports point to the intravenous and oral administration routes [18, 24, 26, 30]. Corticosteroids were reported to induce bronchospasm in asthmatic patients who are allergic to aspirin [31, 32]. Thus, such allergic hypersensitivity reactions should be considered in asthmatic patients with clinical deterioration and bronchospasm despite corticosteroid treatment [31, 32].

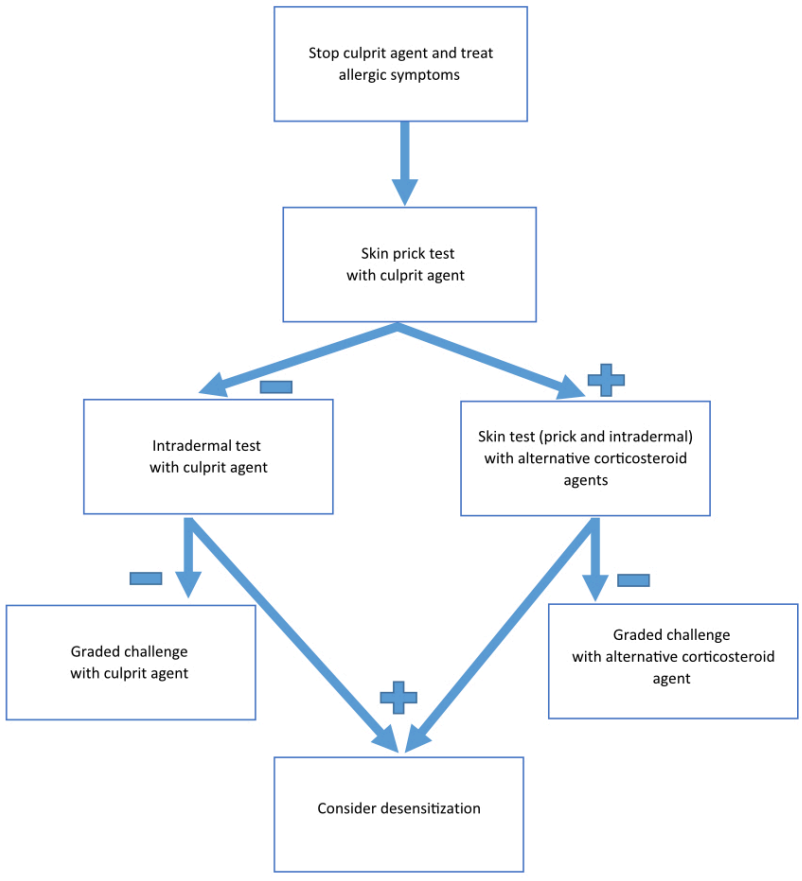
The diagnosis of an immediate hypersensitivity reaction to corticosteroids is based on clinical history and physical examination at the time of the suspicious event. The signs and symptoms of the allergic reaction may resemble those of the basic disorder of the patient (e.g., urticaria), thus the diagnosis is quite challenging. Skin testing with the culprit agent and with possible alternative corticosteroids is recommended (fig. 2).

Skin testing should be started with skin prick test and if the results are negative an intradermal test is indicated. All skin tests must include positive (histamine) and negative (saline) controls as well as the preservatives and excipients (e.g., E466 carboxymethyl cellulose [CMC], polysorbate, polyethylene glycol) or local anaesthetic agents that were given at the time of the allergic event, concomitantly with the suspicious culprit agent. Skin tests (prick and intradermal) for corticosteroids were reported to be safe, without systemic allergic reactions [20] (fig. 3).

The specificity and sensitivity of skin tests for immediate corticosteroid allergic hypersensitivity is not established. Moreover, as discussed above, some of the immediate allergic hypersensitivity reactions to corticosteroids are not IgE-mediated or caused by a corticosteroid hapten (binding to cutaneous or serum proteins to form the allergic antigen), but not by the corticosteroid itself [8]. Thus, the skin test maybe negative in spite of the hypersensitivity. Therefore, a negative skin test (prick and intradermal) does not exclude corticosteroid allergic hypersensitivity. Thus, following negative skin tests (prick and intradermal), graded challenge, under close observation, is the gold standard for confirming or refuting immediate hypersensitivity to corticosteroids.

In-vitro tests for the diagnosis of immediate corticosteroids hypersensitivity are not available for routine clinical usage. However, the basophil activation test (CD203c expression following in-vitro exposure of basophils to the culprit corticosteroid) may be helpful in the diagnosis of corticosteroid immediate hypersensitivity [33].

**Figure 2:** Procedure in the case of clinical suspicion of immediate hypersensitivity reaction to a corticosteroid.



Venturini et al. [18] reported positive skin tests (prick and intradermal) in six out of seven patients with immediate reactions to corticosteroids. Four patients reacted with the culprit agent and the other two with the additive carboxymethyl cellulose. All three patients with anaphylaxis were found to have a positive skin test [18]. Sousa et al. [24] reported four children with corticosteroid-induced anaphylaxis. All patients had positive skin tests (two by prick and two by intradermal tests) to the culprit corticosteroid. A more recent study demonstrated positive skin tests in seven out of eight patients with corticosteroid induced anaphylaxis and in one out of four patients with corticosteroid-induced urticaria. Skin tests of patients who presented with presyncope or flushing were all negative. In the latter study, one case with a false positive and another case with false negative skin tests were reported [20]. Taken together, it appears that skin tests are valuable in the diagnosis of corticosteroid-induced anaphylaxis. The efficacy of skin tests in the diagnosis of other forms of immediate hypersensitivity to corticosteroids is not yet defined.

Treatment of immediate allergic reactions to corticosteroids is based on administration of intravenous fluids, adrenaline and antihistamines. When indicated, oxygen with or without airway opening should also be given [34]. Exposure to the culprit corticosteroid (as defined by the clinical history, skin test or graded challenge) must be avoided. Alternative, safe, corticosteroid agents should be used for future treatment. As discussed above, the cross-reactivity between different corticosteroid classes (or within the same class) for immediate hypersensitivity reaction is not established [8, 10, 11, 21]. Thus, the safety of the alternative agent should be defined by negative skin tests and a negative graded challenge test. Corticosteroids such as betamethasone, dexamethasone or the new steroid agent deflazacort, that were shown to be less allergenic can be considered as alternative agents (following negative skin tests and challenge) [28]. In patients without an alternative safe corticosteroid agent or when challenge is avoided owing to history of severe corticosteroid-induced anaphylaxis, desensitisation to the culprit corticosteroid can be considered (see fig. 3). This procedure should be under close clinical observation and it is only temporarily effective (as long as the patient is receiving the drug). Thus, it must be repeated every time that the patient needs corticosteroid treatment [28, 35, 36].

**Figure 3:** Positive intradermal test for methylprednisolone as part of evaluation of immediate hypersensitivity reaction. Positive and negative controls are included in the test.

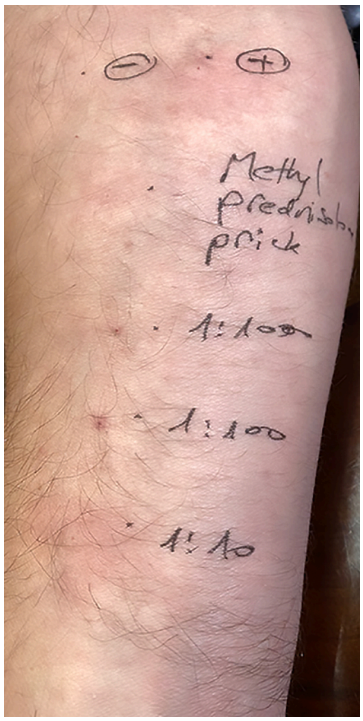
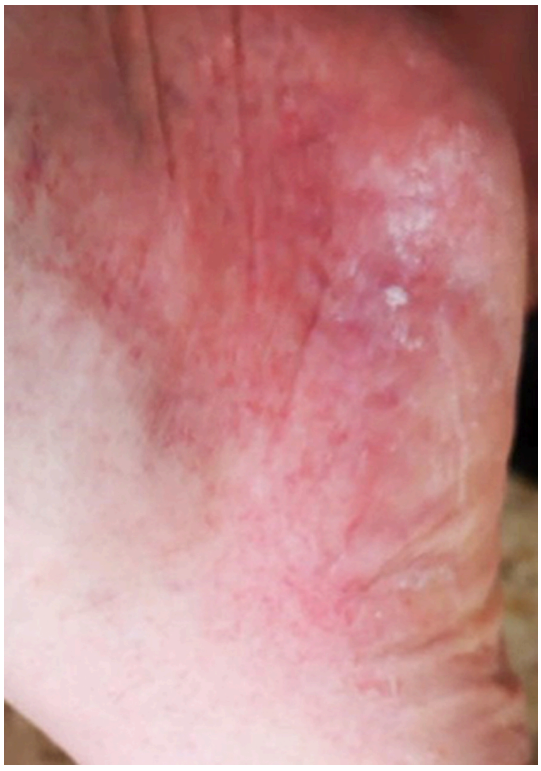



**Figure 4:** Contact dermatitis of the foot – delayed-type hypersensitivity few days after treatment with prednisolone acetate 0.5%.

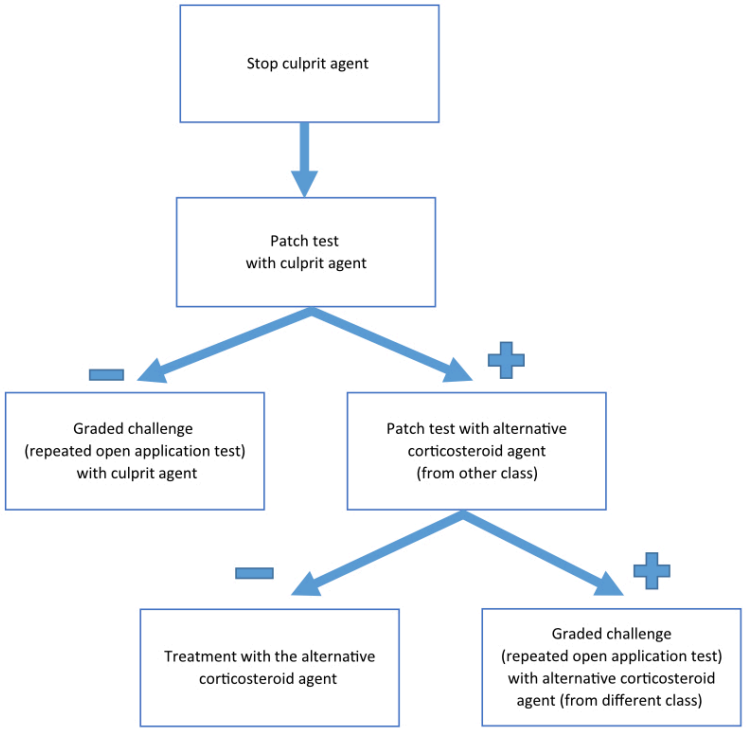


## Delayed hypersensitivity reactions

The most common delayed hypersensitivity reaction to corticosteroids is allergic contact dermatitis, which appears following topical corticosteroid treatment [8, 12] (fig. 4). It presents more than 1 hour and up to a few days following corticosteroid exposure as local or systemic erythema/eczema [10, 12, 21, 37–39].

Less often, exfoliative dermatitis, erythema multiforme, acute generalised exanthematous pustulosis (AGEP) or postural reactions have been reported [8, 10, 11]. Chronic dermatitis, atopic dermatitis, leg stasis and ulcers were shown to be risk factors for topical corticosteroid-induced contact dermatitis. This is, most probably, due to chronic long-term corticosteroid usage in these situations, and to the high penetration and degradation (leading to a higher protein binding rate) of the corticosteroid via the inflamed skin [8, 19]. Delayed hypersensitivity reactions were also reported in patients following inhaled, intranasal or ophthalmic corticosteroids, presenting as facial, perinasal or periorbital erythema with oedema, respectively [40, 41].

**Figure 5:** Procedure in the case of clinical suspicion of delayed hypersensitivity reaction to a corticosteroid.



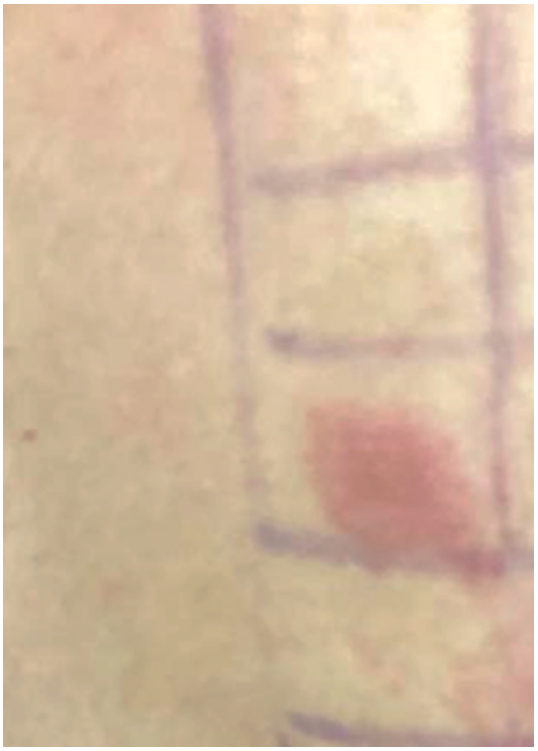

Generalised contact dermatitis was also reported following oral or intraarticular corticosteroid treatment [42].

The diagnosis of corticosteroid-induced delayed hypersensitivity, especially following topical use, is quite difficult since the allergic contact dermatitis may be similar to the basic skin disease of the patients. Thus, in all patients with worsening of their skin disease following the initiation of corticosteroid treatment or in patients who recovered rapidly after corticosteroids withdrawal, allergic contact dermatitis due to corticosteroids should be considered [10, 19, 43]. Indeed, Gonul et al. reported that 22% of patients with contact dermatitis who did not respond to topical corticosteroids had a positive corticosteroid patch test [44]. Occasionally, the local allergic contact dermatitis is more prominent at the edge of the topical corticosteroid application areas ("edge effect"). This may result from the high concentration of the culprit agent at the centre of the area (more anti-inflammatory effect), whereas at the edge where its concentration is lower, the allergic reaction can be manifested. Such phenomena can also be observed in early reading (24–48 hours) of a corticosteroids patch test [10]. Upon clinical suspicion, discontinuation of the culprit corticosteroid followed by diagnostic procedures are indicated (fig. 5). In vitro diagnostic tests, such as lymphocyte transformation or interferon-gamma (IFN-γ) assays, are not validated and are not available for clinical practice [9]. Skin prick tests (always negative) are useless for the diagnosis of delayed hypersensitivity to corticosteroids [38]. Intradermal tests should be avoided since they may cause skin atrophy [38].

Patch testing (a commercial or ethanolic self-made preparation is the standard method for the detection and diagnosis of delayed hypersensitivity to corticosteroids (fig. 6) [6, 10, 11, 19, 38, 43 ]. It should be noted that the delayed hypersensitivity reaction to a corticosteroid agent can be due to additives (vehicles) such as lactose, carboxymethyl cellulose, polyethylene glycol, parabens, fragrance and sorbitan sesquioleate within the corticosteroid preparation [11]. Thus, the appropriate vehicle should be included in the patch test, especially in patients with convincing history of corticosteroid-induced delayed hypersensitivity but a negative patch test to the pure culprit agent [11]. Patch tests should obviously include the suspected culprit corticosteroid as well as agents from the same and other corticosteroid classes (table 1). Patch test should be removed after 48 hours and read on days 2, 4 and 7 [10, 11, 21, 43, 45].

Delayed hypersensitivity to corticosteroids is usually not drug specific, thus, co-sensitisation or cross-reactivity between agents from the same class or even from different classes is common (table1). Some patients with delayed hypersensitivity to corticosteroids are sensitised to the lateral chain(s) of the culprit corticosteroid molecule. Therefore, those patients are also sensitised to other corticosteroids (with similar structure) of the same class (table 1) [19, 21]. In these cases, following a negative patch test with corticosteroid agent(s) from other classes, alternative corticosteroid(s) can be offered (see fig. 5). Other patients are sensitised to the skeletal structure of the corticosteroids. These patients demonstrate a high rate of cross reactivity within and between the corticosteroid classes (table 1) [21]. Thus, extensive patch test workup with different corticosteroid preparations from different classes are needed in order to find a safe alternative corticosteroid medication [6, 21]. According to patch test results, a graded challenge (including repeated open application tests) to the suggested alternative corticosteroid agent is mandatory in order to avoid hypersensitivity reactions.

**Figure 6:** Positive European standard patch test in a patient with a delayed hypersensitivity reaction to budesonide



Baeck et al. reported 315 patients with delayed hypersensitivity to corticosteroids [19]. The higher rate of positive patch tests was found for class A, followed by class B and then class D1 corticosteroid medications. Similar results were observed by Pratt et al., reporting patch tests of 741 patients with corticosteroid-induced delayed hypersensitivity reactions [45]. It should be noted that about 40% of patients with corticosteroid-induced delayed hypersensitivity reactions had a positive patch test to more than one class of corticosteroids, 6% of them reacted to corticosteroids from all five classes, demonstrating a high rate of cross-reactivity [19].

The North American Contact Dermatitis Group reported that 741 out of 17,987 (4.12%) patients who underwent patch tests were positive for corticosteroid medications [45]. Accordingly, the European Society of Contact Dermatitis (ECDS) recommend the use of tixocortol pivalate 0.1% (class A) and budesonide 0.01% (class B) in all standard patch test series [6, 46].

## Conclusion

To conclude, physicians of all medical disciplines should be aware that corticosteroids can cause (“paradoxically”) immediate or delayed allergic hypersensitivity reactions. The diagnosis of such allergic reactions is challenging since it is often difficult to distinguish between hypersensitivity reactions and the deterioration of the basic inflammatory disease (e.g. worsening of asthma or dermatitis). Thus, a high index of suspicion is needed in order to identify the culprit corticosteroid and to find an alternative safe corticosteroid medication.

**Potential competing interests**

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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