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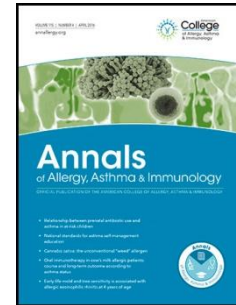
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1 Eczema Complicated by Allergic Contact Dermatitis to Topical Medications and
2 Excipients

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24 sensitivity; topical corticosteroid; corticosteroid allergy; inhalant steroid allergy; topical
25 corticosteroid allergy; corticosteroid hypersensitivity; patch testing; chronic venous leg
26 ulcers; stasis dermatitis

27
28 Abbreviations:

29 ACD – Allergic Contact Dermatitis

30 TCS – Topical Corticosteroids

31 CVLU – Chronic Venous Leg Ulcers

32 SCD – Systemic Contact Dermatitis

33 TEWL – Transepidermal Water Loss

34
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Introduction

In patients with eczema that is difficult to manage, it is important to consider the possibility that they are allergic to the topical medications or emollients being used to manage their skin disease. This group of patients may have allergic contact dermatitis (ACD) to topical corticosteroids (TCS), antibiotics, or the excipients and preservatives used in their topical medications or emollients being used for skin care. For this group of patients, topical corticosteroids or the excipients in their vehicle may actually worsen their underlying disease and are the focus of this article. Those that are more at risk are usually patients requiring long-term treatment with topical corticosteroids, such as patients with atopic dermatitis (AD), and chronic venous leg ulcers (CVLU) or stasis dermatitis.¹

Contact dermatitis (CD) should be considered in the differential diagnosis of severe AD as it may appear similar, or exacerbate underlying AD. CD to corticosteroids is especially important to recognize since TCS are the mainstay of AD treatment.

Role of Atopy in Contact Dermatitis

The role of AD as a predisposing factor to CD is controversial, with a recent pooled-analysis showing no significant difference in contact sensitization between individuals with AD and those without AD.³ However, when looking at general population studies, contact sensitization in AD individuals occurred at greater rates than the general population.³ Due to intrinsic skin barrier abnormalities and more frequent exposure to topical medications individuals with AD may be more vulnerable to CD.⁴⁻⁵ AD patients

69 have impaired skin barrier function, which not only is characterized by increased
70 transepidermal water loss (TEWL) but may also increase allergen and irritant
71 penetration.¹

72
73 Another factor in increased sensitization to contact allergens is that AD patients are
74 exposed to numerous topical medications when compared with normal individuals.⁵ This
75 exposure is often long term as many patients first present with symptoms of eczema in
76 infancy.⁶ Additionally, this exposure is often daily as they manage treatment for their
77 chronic disease. This repetitive application of topical medications and emollients often
78 results in exposure to sensitizers such as fragrances and preservatives, and can result in
79 sensitization to the corticosteroid itself. In 2008, Coloe et al identified vehicle ingredients
80 from the package inserts of TCS that were widely sold in the United States from 2005 to
81 2006. They reported the most common vehicle allergens present in 166 TCS products
82 including generic and branded products as propylene glycol, sorbitan sesquioleate,
83 formaldehyde-releasing preservatives, parabens, methylchloroisothiazolinone/
84 methylisothiazoiinone (MCI/MI), lanolin, and fragrance. Presence of allergen was not
85 correlated with patch test results, and some of the allergens, such as MCI/MI and
86 fragrance are not commonly ingredients in topical medicaments though they may be
87 found in emollients and other personal products.⁷

88
89 In a study of 641 children with AD who underwent patch testing to 7 topical AD
90 treatments (chlorhexidine, hexamidine, budesonide, tixocortol pivalate, bufexamac,
91 sodium fusidate and their current emollient), 6.2% had positive patch tests, with 47.5% to

their emollient, 42.5% to chlorhexidine, and 2.5% to tixocortol.⁸ Risk factors in patients with AD associated with sensitization to their topical treatment products, include more severe and longer duration of illness, onset of AD before 6 months, presence of IgE mediated sensitization, and multiple contact sensitizations to other allergens, especially metal salts.⁸⁻⁹ Interestingly, the children with AD and contact sensitization were also significantly younger (<3 years) than the children with AD and without sensitization, which is consistent with other studies of children with contact sensitization with or without AD.^{8,10} The increased sensitization in those with early onset AD, suggests those with increased sensitization may be more likely born with innate skin barrier abnormalities.⁴

Epidemiology

The incidence of CD to corticosteroid is documented in many studies and ranges from 0.5-5%; however, incidence may vary based on population, duration, and type of underlying dermatitis.^{1, 8,10-11} For example, it may be as high as 40% in CVLU patients or as high as 22% in patients who fail to respond to TCS treatment for ACD.⁹ Tixocortol pivalate, which is a Type A corticosteroid cross-reactive with hydrocortisone, is the most common corticosteroid causing contact allergy, though it is only available for application on mucosal surfaces (nasal sprays, lozenges) in most countries.¹²⁻¹³ In a recent small cohort of 27 patients, budesonide was the most common steroid allergen.⁹ The incidence of CD to tixocortol has been 2-3% in multiple studies looking at cutaneous sensitization via patch testing.^{8,10} However, the data is conflicting, and in other studies the incidence of contact sensitivity to corticosteroids is zero or marginal.^{3,13}

Allergy to Inhaled and Intranasal Steroids

Allergy to corticosteroids can also be seen to inhaled and intranasal steroids though there are no studies looking specifically at patients with AD. Symptoms of inhalant or intranasal allergy vary from immediate hypersensitivity resulting in systemic contact dermatitis (SCD) to a delayed hypersensitivity resulting in airborne CD presenting with eyelid and facial eczema, or even oropharyngeal symptoms and swelling.^{1,13-14} The most frequently implicated inhalant sensitizer is Budesonide, which is cross-reactive with other corticosteroids in the B and D2 group.¹³ Budesonide has been shown to cause contact allergy with personal use, and with airborne exposures in the home and workplace.¹³⁻¹⁴ It is important to note that in the case of Budesonide allergy, other inhalation corticosteroids such as beclomethasone, mometasone and fluticasone derivatives may, in most cases, still be used, since they do not cross-react with budesonide

One study of 30 adults using inhaled or intranasal corticosteroids highlights the importance of patch testing to the vehicle and preservatives in the corticosteroid. In this study, patch testing was performed to the corticosteroids, as well as propylene glycol, and benzalkonium chloride. Benzalkonium chloride is a preservative used in most nasal sprays and eye drops, and was responsible for half of the positive PT reactions in this cohort.¹³ Propylene glycol was not responsible for any of the reactions in this study; however, propylene glycol allergy should be considered when evaluating a patient for allergy to TCS, as it is a common excipient in many emollients and anti-inflammatories.

Clinical Features of Topical Corticosteroid Allergy

Typical symptoms of contact dermatitis to corticosteroids may be recalcitrant disease, atypical appearance or localization of rash or aggravation without known cause.^{1, 15}

When evaluating the more severe recalcitrant AD patient, one must also consider corticosteroid resistance.¹⁶ It is difficult to distinguish corticosteroid allergy with corticosteroid resistance, which would be better defined as failure of AD to improve with use of highly potent TCS, or prolonged use of mid-potency TCS. Recent studies suggest corticosteroid resistance may be attributed to colonization with *staphylococcus aureus*.¹⁶

Mechanism and Classification of Topical Corticosteroid Allergy

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.¹⁷ ACD is a hapten-mediated process whereby antigen specific T-cells are typically activated by cutaneous exposure to haptens in sensitized individuals. This activation occurs in 2 phases, the sensitization phase, and the elicitation phase.⁵ The metabolites of corticosteroids are steroid glyoxals or 21-dehydrocorticosteroids, which are haptens that are lipophilic and bind with skin or serum proteins to induce a hypersensitivity reaction.¹⁸

Non-halogenated, non-methylated topical steroids, such as hydrocortisone and budesonide, are more frequent sensitizers than halogenated molecules, which contain a C₁₆-methyl group.¹⁸ The reasons for this allergenicity can be attributed to ease of hydrolysis of non-methylated C₂₁-corticosteroid esters, allowing them to bind amino

acids, particularly, arginine to form immune complexes that can penetrate into the epidermis and cause delayed hypersensitivity.¹⁸

Corticosteroids are classified according to Coopman classification based on chemical structure.¹² The 4 groups identified were (are), Group A (hydrocortisone type), Group B (acetonides), Group C (Betamethasone type-non esterified), and group D (esters). Group C is considered the least allergenic.¹⁸ Group D, was later divided into 2 groups D1, the ‘stable’ esters, and D2, the ‘labile’ esters.¹⁸ In 2011, Baeck et al. proposed another classification system for topical corticosteroids based on methylation patterns and allergenic profiles derived from patch testing. They divided the corticosteroids into 3 groups (see Table 1): Group 1 are the non-halogenated group and is comprised of steroids from Group A, D2, and Budesonide from the Coopman Classification; Group 2 contains halogenated molecules, and includes steroids from Group B of the Coopman Classification; and Group 3, which are the halogenated molecules are the least allergenic, and includes steroids from Group C and D1.¹⁸ This classification based on allergenic potential, rather than chemical structure may better help to identify cross-reacting corticosteroids.

Excipient Allergy

Allergy to corticosteroids may be to the corticosteroids themselves, or excipients used within the vehicle of the topical preparation.^{2,15}

Propylene glycol, a common ingredient in topical preparations of corticosteroids, is known to cause burning, and stinging, and sensitization, resulting in intolerance to the topical preparation. Hence, propylene glycol earned the title of “Allergen of the Year” from the American Contact Dermatitis Society for 2018.¹⁹ However, the problem of this excipient has been long recognized. In 1991, Catanzaro et al compiled a list of propylene glycol-free topical corticosteroids which we have updated and grouped according to potency (see eTable 2).²⁰ In 2008, Coloe et al identified propylene glycol in 64% of TCS.⁷ Propylene glycol is also found in other topical anti-inflammatories including some topical calcineurin inhibitors (TCI), phosphodiesterase 4 (PDE4) inhibitor, as well as commonly used “bland” emollients. Burning and stinging is a common side effect of propylene glycol.

Patch testing to propylene glycol can help elucidate whether allergy is to the corticosteroid itself or excipients in the vehicle. At higher concentrations (>20% in water), propylene glycol is known to cause skin irritation, which can be seen as an irritant or weak positive reaction on patch tests.²¹ Clinically this may manifest as an irritant CD as a result of the excipient and may be confused with a contact sensitivity to corticosteroids.²¹

Several studies have identified additional excipients present in topical pharmaceutical and personal care products, including lanolin or wool alcohols, sorbitan sesquioleate, parabens, and cetyl stearyl alcohol.^{7,22} Sorbitan sesquioleate, and its cross-reacting substances, including polysorbates and sorbitan monostearate have been found 28% of

TCS, making them the second most common excipient allergen present in TCS. However, its clinical relevance as an allergen is significantly less as only 0.8% of patients in one cohort were found positive to sorbitan sesquioleate on patch testing.⁷ There have been isolated case reports of allergy to additional excipients found within various corticosteroids; however, propylene glycol remains the most common cause of topical medicament excipient allergy.

Diagnosis

Contact sensitivity to corticosteroids should be suspected based on history of usage and chronology of symptoms. Patch testing is the standard for diagnosis of contact sensitivity to corticosteroids and excipients. It is recommended to patch test with corticosteroid markers, rather than all available corticosteroids, as well as all TCS the patient is using. The commonly used TCS for patch testing are tixocortol pivalate, budesonide, and hydrocortisone-17-butyrate. For details on patch testing, to TCS please see “Contact Dermatitis and Patch Testing for the Allergist” in this issue.

When interpreting patch test results, it is important to note that if patch tests show allergy to a specific topical steroid, it is likely that the patient will also be allergic to others. Propylene glycol is commonly patch tested with a 30% aqueous dilution, though it is also commercially available in 5% petrolatum. We recommend interpreting results at 48 hours and 72-96 hours with cautious interpretation due to its weak sensitizing and irritant potential.¹⁹

Management:

The management of eczema should always include use of bland emollients with as few irritants and sensitizers as possible, including avoidance of fragrance, and formaldehyde and its releasers, which are common additives in personal care products. Antiseptics should be used cautiously as they may be frequent sensitizers, especially in children with AD.⁸

The management of corticosteroid allergy includes identifying the allergen, as well as treating the underlying dermatitis. It is paramount to switch TCS to a different group if allergy to TCS is identified; or switch to treatment with TCI or PDE4 inhibitor being mindful that some excipients, particularly propylene glycol are common to many topical anti-inflammatories. In cases of suspected excipient allergy, providers should select topical products with a different excipient or vehicle base for the patient.

Conclusions

Topical medication allergy should be considered in those patients with recalcitrant dermatitis, particularly pediatric patients with AD with early onset disease who fail to respond or worsen on typical treatments and those with stasis dermatitis or chronic leg ulcers. This is true of pediatric patients even if they are younger in age than their non-allergic counterparts. In both groups, the chronic dermatoses result in use of prolonged topical medications, particularly corticosteroids increasing the risk of sensitization due to duration of disease. The most common TCS allergen is tixocortol, which is used as a

marker for hydrocortisone. Hydrocortisone is readily available over-the-counter and is used ubiquitously creating frequent opportunities for sensitization in the at-risk patient.

In patients with severe AD, who fail to respond to treatments, one should also consider excipient allergy, and consider patch testing to confirm the diagnosis. There are currently no other tests for the diagnosis of topical medication or excipient allergy. In the cases of diffuse eczema, where patch testing is not practical, one may consider empirically changing selection of topical regimen based on clinical suspicion. We recommend, avoiding known contact allergens, such as the non-halogenated corticosteroids, and eliminating use of propylene glycol in these more severe patients. Modification of topical agents should be tried before considering management with more costly biologics or immunosuppressants with associated toxicities.

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327 Table 1: Baeck Classification of Topical Corticosteroids
328

Group 1	Group 2	Group 3
non-methylated, most often non-halogenated molecules (groups A and D2, and budesonide)	halogenated molecules with C16/C17 cis ketal/diol structure (group B or acetonide group)	halogenated and C16-methylated molecules (group C and D1)
Cloprednol	Amcinonide	Betamethasone
Cortisone acetate	Desonide	Betamethasone sodium phosphate
Dichlorisone acetate	Fluchloronide	Desoxymethasone
Fludrocortisone acetate	Flumoxonide	Dexamethasone
Fluorometholone	Flunisolid	Dexamethasone acetate
Fluprednisolone acetate	Fluocinolone acetonide	Dexamethasone sodium phosphate
Hydrocortisone	Fluocinonide	Diflucortolone valerate
Hydrocortisone acetate	Halcinonide	Diflorasone diacetate
Hydrocortisone 21-butyrate	Triamcinolone	Flumethasone pivalate
Hydrocortisone hemisuccinate	Triamcinolone acetonide	Fluocortin butyl
Isofluprednone acetate	Triamcinolone benetonide	Fluocortolone
Mazipredone	Triamcinolone diacetate	Fluocortolone caprylate
Medrysone	Triamcinolone hexacetonide	Fluocortolone pivalate
Methylprednisolone acetate		Fluprednidene acetate
Methylprednisolone hemisuccinate		Halomethasone
Prednisolone		Meprednisone
Prednisolone caproate		Alclomethasone dipropionate
Prednisolone pivalate		Clobetasol propionate
Prednisolone sodium metasulphobenzoate		Clobetasone butyrate
Prednisolone succinate		Fluticasone Propionate
Prednisone		Mometasone Furoate
Tixocortol pivalate		

Budesonide		
Ciclesonide		

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Table 2. Topical Corticosteroid Potencies, Strengths, and Formulations without Propylene Glycol

Class I: Superpotent/ Very High Potency		
Class IV: Mid-Strength/ Medium Potency		
Betamethasone dipropionate (ointment)		Desoximetasone, 0.05% (cream,
Diflorasone diacetate, 0.05% (ointment)		Fluocinolone acetonide, 0.03%
(Synalar ointment) Flurandrenolide, 0.05% (Cordran Tape)		Triamcinolone acetonide, 0.1%
(Aristocort cream)		
Desoximetasone, 0.25% (spray)		Triamcinolone acetonide, 0.1%
ointment		
(ointment)		Flurandrenolide, 0.05%
Class II: Potent/ High Potency		
Class V: Lower Mid-Strength/ Lower-Medium Potency		
Betamethasone dipropionate, 0.05% (cream)		Desonide, 0.05% (ointment, Tridesilon cream)
Desoximetasone, 0.25% (cream)		Hydrocortisone butyrate, 0.1% (cream,
ointment)		
Desoximetasone, 0.05% (gel)		Triamcinolone acetonide, 0.025% (ointment)
Diflorasone diacetate, 0.05% (ointment)		Flurandrenolide, 0.05% (Cordran lotion)
Halcinonide, 0.1% (ointment, solution)		
Amcinonide 0.1% ointment		
Class III: Upper Mid-Strength/ Medium Potency		
Class VI: Mild/ Low Potency		
Betamethasone valerate, 0.12% (Luxiq foam)		Fluocinolone acetonide, 0.01% (oil)
Betamethasone valerate, 0.1% (ointment)		Desonide, 0.05% (Verdeso foam)
Triamcinolone acetonide, 0.5% (ointment)		
Class VII: Least Potent/ Lowest Potency		
(Hytone ointment, Lacticare lotion,		Hydrocortisone 2.5%
		Nutricort lotion)
		Hydrocortisone 1% (Hytone
		ointment, Cortizone 10
		Maximum)