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A Review of Contact Dermatitis

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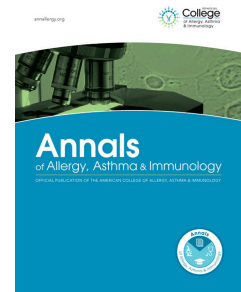
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Abbreviations: ACD, allergic contact dermatitis; AD, atopic dermatitis; benzisothiazolinone, BIT; CAPB, cocoamidopropyl betaine; CAMP, Contact Allergen Management Program; CD, contact dermatitis; FLG, filaggrin; formaldehyde releasing preservatives, FRP; ID, irritant dermatitis; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; North American Contact Dermatitis Group, NACDG; octylisothiazolinone, OIT; PG, propylene glycol; SD, stasis dermatitis; Repeated open application test, ROAT; SCD, systemic contact dermatitis; TCS, topical corticosteroids

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Objective Reading this article will familiarize the reader with the mechanisms and causes of contact dermatitis.

Data Sources Recent research articles, relevant review articles, and case series/reports in English from PubMed database mostly from 2010 onwards.

Study selections Most data was in the form of retrospective studies. Efforts were made to include clinical trials; however, for newer allergens and data on biologics, case series and case reports were included. Older studies regarding mechanism were included if they were of particular importance.

Results An understanding of this review should enable the reader to approach the patient with unknown dermatitis with a better understanding of cause and management. **Conclusion** Clinical suspicion for relevant allergens combined with interpretation of patch tests are important in the diagnosis and treatment of patients with contact dermatitis.

1 **Introduction**

2 Contact dermatitis (CD), or dermatitis attributed to “outside” allergens or irritants is a
3 skin disorder often attributed to occupational skin exposures making it the most common
4 occupational skin disease.¹⁻² Apart from occupational exposures, the increased, and
5 frequent use of cosmetics and personal care products are an additional risk factor for the
6 development of CD, particularly in women.³⁻⁴ The use of multiple cosmetic products has
7 become a widespread trend, with the advent of “influencers” promoting the use of
8 multiple cleansers, and products, such as double-cleansing, and 10-step skincare routines,
9 which result in increased exposure to sensitizers. These routines alter the skin
10 microbiome, and may lead to breakdown of the superficial layers of the skin increasing
11 allergen penetration.⁴

12 Patch testing is the gold standard for the diagnosis of ACD; however, correlation of
13 history and physical examination are paramount in identifying hidden sources of
14 allergens. One should screen for wet/dry cycles that can occur from “wet work”, and also
15 from daily habits, such as constant wiping of the face with wipes and washcloths after
16 infant feeds, hand washing, sweating, and swimming.⁵⁻⁶ These habits of daily living can
17 cause ordinary personal items, such as cell phones, to become releasers of contact
18 allergen, such as metal alloys.⁷

19 In this review, we will highlight newer proposed mechanisms of contact dermatitis,
20 including allergic contact dermatitis (ACD), and irritant contact dermatitis (ICD);
21 highlight relevant contact allergens, particularly for those with concomitant atopic

dermatitis (AD). Additionally, we will review the current literature on therapeutic options in CD, including the role of biologics in the treatment of CD.

Role of Atopy

A systematic review of AD and ACD found that AD patients had higher rates of patch test positivity than the general population, though positive patch tests were still lower when compared with the population specifically seeking out patch testing.⁸⁻⁹ AD skin may be hyporesponsive to allergens due to baseline immune programming that prohibits the typical Th1 responses seen in response to contact allergens; and there may be attenuated responses in AD skin to typical sensitizers.¹⁰⁻¹¹ Gitler et al propose that patients with atopic dermatitis and elderly patients may also be more susceptible to ACD and ICD due to a compromised skin barrier.¹² Individuals with AD are exposed to numerous products on a daily basis, often from an early age. Due to these exposures they may be at increased risk for sensitization from these products including topical corticosteroids (TCS), and “bland” emollients, as they may still contain allergens, such as propylene glycol, sorbitans, lanolin, fragrance, and preservatives.¹³ In the elderly population, relevant allergens may be fragrance mix, nickel, and Balsam of Peru, and dermatitis may appear as a stasis dermatitis (SD) or as chronic venous leg ulcers, rather than a more typical localized CD.¹⁴

Additionally, some studies suggest increased filaggrin loss-of-function mutation (FLG) in CD, particularly with nickel sensitization, and in hand eczema, which is a phenotype that may represent contributions of both atopic and contact dermatitis.¹⁵⁻¹⁸ There are other studies; however, that suggest no such association, and that responses to allergens are not changed in individuals with FLG mutation.^{11-12,19}

Mechanism

Our current understanding of allergic contact dermatitis, is that of a 2-phase process, that begins with “sensitization” with a low-molecular weight allergen or hapten, which is presented by dermal dendritic cells (DCs) to T-cells in a proximal draining lymph node.^{1,2,20} The DCs involved in hapten recognition and pathogenesis are thought to be Langerhans cells, or myeloid DCs, which produce IL-1 β .^{1, 21} The sensitization phase results in the production of effector T-cells, which in the 2nd phase, the elicitation phase, produce a dermatitis, which develops approximately 72 hours after re-exposure to the offending allergen.

This Type IV delayed-type-hypersensitivity response was thought to be mediated by Th1 cells, though Th2, Th17, and Th22 cells may also play a role.^{1,10, 22} Clinically, the dermatitis manifests as itching, erythema, vesicles, papulation, and oozing. Newer studies suggest, the immune signaling pathway may be antigen-dependent. Molecular profiling of inflamed skin samples revealed allergen-specific differences in the T-cell profile of the skin.¹ Nickel produces a mixed T cell response (Th1/Th2 and Th17), and may send chemokine signals to attract activated type 1 memory T cells to the site of nickel exposure.^{1, 23} Other allergens, such as fragrance may cause Th2/Th22 polarization, similar to the immune process of severe AD, which is particularly interesting as fragrance may be a relevant allergen in pediatric AD.²⁴

In murine models of contact hypersensitivity, IL-25, which is implicated in the atopic march, may also potentiate Th17-mediated skin inflammation in the elicitation phase.²² In skin biopsy samples of nickel contact hypersensitivity, there is also increased Type 2

chemokine signaling, regulated by IL-4, which attracts, CCR4-Th2 cells and eosinophils to the site of dermatitis.²³ This suggests that in allergic disease states, where type 2 inflammation predominates, such as AD, mechanisms of CD may also be enhanced.

In a study by Newell et al, individuals with AD who underwent chemical sensitization with 2,4-dinitrochloro- benzene (DNCB) had resultant Th2-skewed immune response, which persisted even 3 months after exposure.¹¹ Nedorost and colleagues suggest that such programming may also be responsible for drivers of the allergic march in children with early onset protein-contact dermatitis related to skin irritation from factors, such as drooling and saliva irritation.⁶ Irritant contact dermatitis (ICD) is a result of skin irritants causing damage to the epidermal layer of skin, which results in destruction of keratinocytes.^{12,15} Keratinocytes release cytokines, such as IL-1a, IL-1b, IL-6, IL-8, TNF- α resulting in activation of the innate immune system.¹²

Clinically and histologically, ICD and ACD may be difficult to distinguish. Frings et al examined pathology of skin biopsies of patients with confirmed ACD, ICD and AD; using predictive modeling approaches they found necrotic epidermal keratinocytes to be associated with ICD, and focal parakeratosis (retained nuclei of keratinocytes in the stratum corneum) to be associated with ACD.²⁰ There were also increased NK cells in the epidermis in ICD, and pseudo-Pautrier microabscesses containing myeloid DCs (CD11c⁺) in ACD.²⁰ Eosinophils in the dermis, which is a finding attributed to ACD, was found more commonly in AD samples in their study.²⁰ Other findings of ACD include spongiosis, and intraepidermal vesicles; clusters of T-cells and DCs have been identified in the dermis beneath these lesions.^{1,2}

Clinical Features

Clinically, ACD and ICD may appear as a well-demarcated pruritic rash, which in the acute phase may appear as bright-red erythema, and edema; blistering, weepy, and vesicular rash are findings more associated with ACD, and may be confused for a localized skin infection.¹⁻² Chronically, both types of CD may be difficult to distinguish from other forms of eczema, as there may be loss of distinct borders, and lesions may become generalized, lichenified, hyperpigmented, and even violaceous. Overlap of 2 types of eczematous dermatitis may be possible. Variants of localized CD can be seen, such as hand eczema, eyelid dermatitis, cheilitis, airborne contact dermatitis, ectopic dermatitis, where the allergen is transferred from one body part to another; and consort contact dermatitis, where the rash may be the result of allergen contact from someone in close proximity, such as a caregiver or partner. Other forms of CD include systemic contact dermatitis (SCD), and contact urticaria, which will not be discussed in this review.

Allergens

Historically, and presently nickel remains the most common contact allergen. However, sources of other common contact allergens are changing from easily identifiable, such as neomycin; or occurring from noxious environmental exposures to more “hidden allergens”. In the most recent review of patch test results from the North American Contact Dermatitis Group (NACDG), nickel sulfate remained the most common allergen (17.5%). However, the second most common allergen was methylisothiazolinone (13.4%), followed by fragrance mix (11.3%), formaldehyde (8.4%), and

methychloroisothiazolinone (7.3%).²⁶ This indicates that the top allergens are hiding as preservatives and ingredients in everyday products. Additionally, a trend towards use of “natural products” due to fears of chemical toxicity, has resulted in emergence of new allergens, such as essential oils and glucosides. Relevant allergens are discussed below.

Metal Alloys

Nickel

Nickel sulfate is the most common contact allergen, and frequency of nickel sensitivity has increased over time, reaching a prevalence rate of 17.5% in 2015-2016.²⁶ Sensitivity occurs more commonly amongst young, female, non-white, atopic individuals with asthma or eczema.²⁷ Prevalence rates are even higher in the pediatric population, reaching a prevalence rate of 23.7% of children patch tested by the NACDG, occurring more frequently in girls, and those less than 5 years old.²⁸ Typical dermatitis affects the face, scalp, ears, neck, arm, or trunk (periumbilical); though in the pediatric population widespread dermatitis and id reaction can be seen.²⁷⁻²⁹

Jewelry is the most common source of nickel allergy, and risk factors for nickel allergy include having 1 or more piercing with frequency of nickel sensitivity increasing with the number of piercings.²⁹ Other sources of nickel include personal electronic devices, including smart watches, and other wearable technology, snaps and buttons on clothing, buckles, tools, utensils, coins and toys.^{2,18, 28,31}

Nickel is a water-soluble antigen, and in molecular profiling studies of patch test positive skin to nickel, nickel caused the most significant immune reaction resulting in more cellular infiltrates of T cells (CD3 and CD8) and CD11c DCs compared with other allergens.^{1,9} The development of ACD to nickel is due to nickel release, which occurs

from prolonged contact with nickel containing items. The European Chemicals Agency defines prolonged nickel contact as more than 10 minutes on 3 or more occasions within 2 weeks or more than 30 minutes on 1 or more occasions within 2 weeks.³⁰ A recent study showed that prophylactic application of topical corticosteroid prior to nickel exposure minimized the expected reaction in sensitized individuals.³²

Other metals

Other metal alloys, such as cobalt chloride, chromium, and gold thiosulfate may cause allergic contact dermatitis. Cobalt was a top 20 allergen in 2018, while chromium, and gold are less common allergens.³⁻⁴ Potassium chromate is found in leather tanning products, and cement, and may cause foot dermatitis; there may be higher rates of chromium allergy in individuals with AD.⁹

Preservatives

Preservatives are added to personal care products and cosmetics to prevent bacterial growth. However, many preservatives are contact allergens (see Table 1).

Isothiazolinones

Methylisothiazolinone (MI), and Methylchloroisothiazolinone (MCI) are preservatives that have a ubiquitous presence in products. MI alone, which was only added to the North American series (NAS) in 2013-2014 became the second most common allergen for the NACDG, and sensitivity has been increasing in prevalence globally.^{26,33} MI and MCI can be found in isolation or in combination (KathgonTM CG) in cosmetics, personal care products, wet wipes, cleaning products, and school glue. Clinically, isothiazolinones

have caused diaper dermatitis, from use in baby wipes, including from “natural” and sensitive wipes.³⁴ They are an emerging cause of facial dermatitis in men from male grooming products.³⁵ Additionally, multiple cases of hand dermatitis have been reported from homemade slime, which is a conglomerate of school-glue, laundry detergent, Borax, contact lens solution, and shaving cream popular amongst school-aged children.³⁶⁻³⁸ In cleaning products, isothiazolinones, including benzisothiazolinone (BIT) and octylisothiazolinone (OIT) may be found in high concentration, beyond what can be rinsed off.³⁹ In one study of 34 products, 17 of which were selected at random, 76.5% contained at least one isothiazolinone, with MI and BIT most commonly detected via mass spectroscopy.³⁹ BIT is not tested in routine patch test series; thus it needs to be in the index of suspicion for clinicians.³⁹

Parabens

Parabens are preservatives found in topical formulations, personal care products, such as sunscreens, and cosmetics. They are weak sensitizers when compared with MCI/MI, and as such, were named the American Contact Dermatitis Society’s *nonallergen* of the year in 2019 due to their low sensitization rate.³⁻⁴ Parabens may be cross-reactive with para-aminobenzoic acid and para-phenylenediamine (PPD).⁴

Formaldehyde

Formaldehyde is a biocidal preservative used in tissue and cadaveric preservative solutions. It is also found in nail polish, cosmetics, and personal care products. Use in nail polish can result in eyelid dermatitis. Formaldehyde is also found in salon treatments for “Brazilian blowouts”, where its use can cause not only scalp rash, but a generalized

dermatitis. Formaldehyde is also found in wrinkle free clothing and uniforms, where typical rash occurs on the trunk and back with sparing of axillary vault and face. There are also a number of formaldehyde releasing preservatives (FRPs) including, DMDM hydantoin, quaternium-15, imidazolidinyl urea, diazolidinyl urea, and 2-Bromo-2-nitropropane-1,3-diol, with only the latter 4 included in the standard T.R.U.E. test series.⁴⁰ FRP release formaldehyde in the presence of water.⁴¹ Formaldehyde itself can be patch tested at a 1% or 2% concentration, though the 2% concentration may yield more positive results.^{26,42}

Fragrances

Fragrances are mostly synthetic compounds, which are often added to products to create aroma or scent; however, they may also be used in products labeled as “scent-free” with the use of odor-blending fragrances.³ Fragrances are the most common allergens for cosmetic product users (see Table 1), and a particularly relevant allergen for middle-aged women.³ Three fragrance markers are commonly used for patch testing, these include fragrance mix 1, fragrance mix 2, and Myroxylon pereirae, also known as Balsam of Peru.⁴³ Fragrance mix 1 includes isoeugenol, eugenol, cinnamic aldehyde, cinnamic alcohol, hydroxycitronellal, geraniol, a-amyl cinnamic aldehyde and oak moss absolut; whereas fragrance mix 2 includes citronellol, hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrar), hexyl cinnamal, citral, coumarin, and farnesol. These can be cross-reactive with essential oils, though if essential oil allergy is suspected, patch testing with patient’s own products either directly or in diluted form should be performed.⁴³⁻⁴⁴ Patients sensitized to colophony, a tree resin, and propolis, beeswax, that is derived from tree bark can display cross-reactivity with fragrance mixes on patch testing, though the

inverse may not be true.⁴⁵ Balsam of Peru, is also a tree-derived liquid, which contains the antigenic compounds benzyl benzoate and benzyl cinnamate, cinnamic aldehyde, cinnamic alcohol, eugenol, isoeugenol, and vanillin, which can be cross reactive with spices, such as cloves. Additional fragrances, not included in the fragrance series, include linalool and limonene, which create a floral or citrus smell, and are found in many essential oils, such as lavender, ylang-ylang, rosemary, citrus peel, and tea tree oils. These fragrances can oxidize upon exposure to air, such as with sprayed perfumes, and essential oil diffusers, which have become increasingly popular through social media, are sources of potentiated allergen.⁴⁴ Essential oil allergy may not be detected through standard patch test screening using fragrance mixes, and may require patch testing with patient product.⁴³⁻⁴⁴

Excipients

Propylene Glycol

Propylene glycol (PG) is comprised of a propane molecule with a hydroxyl group at position 1 and 2.⁴⁶ It has strong water-attracting properties, and as such is a humectant often used as a vehicle for topical medications, that can help increase the bioavailability of the drug being delivered.⁴⁷ It is more commonly found in cosmetics, personal care products, such as emollients, and is used as an additive in processed foods and oral medications.⁴⁷ PG is the most common allergen found in TCS. PG is also present in other topical anti-inflammatories, such as preparations of pimecrolimus and crisabarole, which are used to treat AD and other inflammatory skin disorders.^{13,48} Patients with PG sensitization are more likely to have atopy, and 20.5% have underlying AD.⁵⁰ PG itself

may be a skin irritant resulting in ICD in patients with already compromised skin barrier. On patch testing, use of patch test concentrations >20% may result in irritant reactions.⁴⁹ PG does not seem to be cross-reactive with its derivatives, such as dipropylene glycol, PG monostearate, PG diacetate, hexylene glycol, pentylene glycol, and butylene glycol.⁴⁶ PG allergy is more common than TCS allergy, ranking as a top 20 allergen in 2015-2016 NACDG data, whereas some of the TCS, such as Clobetasol-17-propionate, and desoximetasone are bottom ranking allergens.²⁶ However, topical steroids are the second most common source of PG responsible for 18.3% of positive reactions, as it is found as an excipient in some very commonly used topical CS.⁵⁰ A list of PG-free TCS is provided in Table 2. Other excipients found in topical steroids, which may rarely cause allergy, are sorbitans, such as sorbitan sesquioleate.¹³

Lanolin

Lanolin is derived from sheep sebum, and found in personal care products, including popular emollients, and as an excipient in a few TCS. They are a relevant allergen in the AD and elderly population, particularly in those with lower extremity venous SD, where sensitization rates may be as high as approximately 19-33% due to a phenomenon known as the “lanolin paradox” where lanolin normally is a weak sensitizer of normal skin, but can sensitize damaged skin more readily.^{13-14,51} The allergenic portion of lanolin is attributed to alcoholic fractions, and as such, wool alcohols or Amerchol, should be used for lanolin patch testing, rather than pure lanolin.⁵¹

Surfactants

Cocoamidopropyl Betaine

Cocoamidopropyl Betaine (CAPB) is a surfactant first formulated for use in a popular baby shampoo in place of the more irritating surfactants sodium lauryl sulfate and sodium laureth sulfate. Allergy may be due to a number of related-compounds created during the manufacturing process, such as, amidoamine, dimethylaminopropylamine, and oleamidopropyl dimethylamine, rather than CAPB itself.⁵² Because of its foaming quality, CAPB is found in a number of cleansing products, especially shampoos, conditioners, body washes, and soaps, including popular bar soaps recommended for sensitive and baby skin.⁵³⁻⁵⁴

Dermatitis distribution can include hand and neck dermatitis, along with hand eczema.

Glucosides

Another group of surfactants emerging as a relevant allergen are alkyl glucosides, which were named as the contact allergen of the year in 2017, and are the third most prevalent surfactant in the Contact Allergy Management Program (CAMP).^{3,55} Examples include, lauryl glucoside, decyl glucoside, cetearyl glucoside, coco glucoside, and caprylyl/capryl glucoside.⁵⁶ They can be found in “natural” biodegradable products, especially household cleaning products and cosmetics. They have also been found in surgical-grade disinfectants, and were the most common allergen in iodine-containing products causing dermatitis in health care workers.^{3,57}

Topical Medications

Antibiotics

Topical antibiotics, such as Neomycin and Bacitracin were previously of greater prevalence, reaching peak prevalence rates of 13.1%, and 9.2% respectively in the late

1990s, compared with 7% and 6.9% in the most recent report of the NACDG from 2015-2016.^{26,58} Nonetheless, Neomycin and Bacitracin were still considered top 10 allergens, that are of particular relevance for older individuals, and individuals with AD.^{2,8} Patch test interpretation for these medications should be read at 7-10 days.² The alternative medication for those allergic to Neomycin and Bacitracin is Mupirocin, which has very limited case reports of contact allergy.⁵⁸

Topical Corticosteroids

TCS allergy may be due to the steroid itself, or an ingredient within the TCS. Steroid allergy is an uncommon entity, though important to recognize given the potential for treatments of CD and AD to potentiate or worsen the underlying disease. TCS allergy should be suspected when dermatitis is unresponsive or worsened by treatment with TCS of appropriate potency for greater than 3 weeks.⁵⁹ The metabolites of steroids, steroid glyoxals are highly lipophilic allergens, which can penetrate the stratum corneum readily.¹³ Patch test interpretation for steroids should be delayed to 7 days due to the potential for initial response to be suppressed by the anti-inflammatory effects of the medication.² A phenomenon, known as the “edge effect” can be seen, where the borders of the patch test site are positive, while the skin within the chamber remains negative (see Figure 1).² There are 5 groups of steroids for patch testing purposes, tested with the following representative allergens: tixocortol-21-pivalate (group A), budesonide (group B), desoximetasone (group C), Clobetasol propionate (group D1), and hydrocortisone-17 butyrate (group D2).² Group A, and budesonide are cross-reactive with group D2, though cross-reactivities can occur across other groups.⁵⁸ Tixocortol is the most common allergen in the United States, likely related to the easy availability of hydrocortisone

ointment, another group A TCS. The rate of tixocortol allergy amongst the general patch test population has remained relatively stable for the past 10 years, occurring at a rate of 2-3%.²⁶ However, in certain groups, such as children with AD, and the elderly with SD, sensitization is more common, and can be as high as 40%.^{13,54} To overcome confirmed or suspected TCS allergy when treating dermatitis, one strategy is to switch to topical calcineurin inhibitors (TCI) for management, or consider use of a biologic for treatment of recalcitrant disease.

Diagnosis

The gold standard for diagnosis of ACD is patch testing. Patch testing should be performed in cases where history and physical create a suspicion for an outside allergen causing a dermatitis. In patients with AD, patch testing may be considered if AD is worsening, or persistent despite topical treatment; if distribution is localized rather than in typical AD distribution, such as in eyelid dermatitis, cheilitis, or hand eczema.⁸ Additionally, patch testing can be considered prior to initiating systemic or biologic treatment to exclude other contributing factors to severe disease, particularly in cases of generalized dermatitis.^{8,54} We recommend patch testing if medications cause burning/stinging that is not a known side effect of that drug.

Patches should be placed on the back, on areas of dry skin, free of moisturizer. Patches are removed after 48 hours, with initial interpretation 30 minutes after removal; and second interpretation of patch test site at 72 to 96 hours.² Patch testing can present problems with reproducibility with repeat testing; in one study of 35 patients to 39 antigens, 44% of reactions were non-reproducible.⁵¹ Additionally, some allergens may require delayed reading up to 7-10 days, such as TCS, or the addition of photo-

sensitization, such as benzophenones, which are found in sunscreen. Use of standardized series, such as the T.R.U.E. test may miss clinically relevant allergens, such as PG, and CAPB. We recommend use of comprehensive standardized series, along with Finn Chambers to test patient's own products to help determine which of their daily exposures is contributing to dermatitis. Alternatively, repeated open application test (ROAT) can also help determine culprit products, and can be performed at home by the patient on test area, such as the posterior ear, or flexural elbow.⁴³

Management

Management of CD, begins with patch testing, which allows for allergen identification and avoidance (see Figure 2), key steps to alleviate dermatitis. Avoidance requires careful label reading for the allergen, and cross-reactive ingredients. Knowledge of these cross-reactive ingredients, and common sources of a particular allergen can help in counseling the patient. Use of patient resources, such as the CAMP from the American Contact Dermatitis Society, and the SkinSAFE application for mobile devices (www.AllergyFreeSkin.com), can guide patients on safe products, though they require provider subscription.⁴ Additionally, some free internet resources have product databases that allow individuals to search or filter out by ingredient, such as the Environmental Working Group's (EWG) Skin Deep[®] Cosmetic Database and the National Eczema Association (NEA) Seal of Acceptance[™] that lists only products deemed safe for people with eczema.

Treatment of CD can be accomplished with use of TCS, and TCI, which are a favored treatment in cases of eyelid dermatitis. For more severe, acute cases with significant

edema, especially of the face, and eyelids, short courses of oral corticosteroids may be used. However, for long-standing chronic ACD, there is emerging evidence for the role of biologics (see Table 3).

In theory, biologic treatment in ACD can be varied and personalized based upon unique allergen polarity.⁶⁰ However, biologics, such as Ustekinumab, which targets the IL-12, and IL-23 pathway, have not been effective in the treatment of ACD.⁶¹ Most data available on Dupilumab in contact dermatitis is in the form of case reports, case series, and retrospective studies of adults. In a retrospective study of 64 patients with AD with and without ACD, improvement in AD was seen despite presence of suspected or patch-test-confirmed ACD, consistent with previous studies showing up-regulation of IL-4 levels in ACD patients.⁶² In other studies of patients with AD with concomitant ACD who were treated with Dupilumab; Dupilumab interfered with patch test results in only a minority of patients.⁶³⁻⁶⁴ Interestingly, in one case report, Dupilumab administration resulted in onset of recall dermatitis at patch test site for colophony, 24 hours after administration, suggestive of non-Type 2 immune pathways contributing to underlying dermatitis.⁶⁵ Clinical trials of Dupilumab in CD and studies in children are needed. Patch testing may be beneficial in patients with severe AD with partial response to Dupilumab, as removal of the offending allergen can provide additional clinical improvement and in some cases resolution of the AD.⁶³⁻⁶⁵

Conclusion

ACD and AD can co-occur and potentiate underlying barrier and immune abnormalities. The barrier compromised skin of individuals with AD, and the elderly with SD may be

356 more sensitized by certain allergens, such as PG and lanolin, which are found as
357 excipients in the products used to manage their underlying skin condition. Additionally,
358 products marketed for children with AD may contain weakly Th2 sensitizing allergens,
359 such as fragrances and CAPB, which affect atopic skin more.^{53,66} In patients with severe
360 AD, who warrant treatment with Dupilumab, patch testing can still be performed, and
361 contact allergen avoidance combined with Dupilumab may provide additional clinical
362 benefit in relief of underlying dermatitis. Patch testing with patient's personal products
363 along with standardized series is recommended.

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

From: Brar KK, Leung DYM. Eczema complicated by allergic contact dermatitis to topical medications and excipients. *Ann Allergy Asthma Immunol.* 2018;120(6):599-602.

Table 1: Notable Preservative and Excipient Allergens

Allergen	Prevalence	Sources	Characteristic Dermatitis	Patch Testing Considerations
Methylisothiazolinone (MI)/ Methylchlorisothiazolinone (MCI)	13.4%/7.3%	Detergents, school glue, wet wipes, cosmetics, cleaners, homemade slime	Hand dermatitis, diaper dermatitis, facial dermatitis	Test MI in isolation in addition to MCI/MI
Fragrance	11.3%	Cosmetics, face cream, antiperspirants, fluocinolone oil	Rash on neck, face, axilla, hands, posterior ears	Cross-reactive with colophony, essential oils, Balsam of Peru
Formaldehyde	8.4%	Brazilian blowout treatment	Scalp rash, generalized dermatitis, trunk/back with sparing of axilla	Should also test for formaldehyde releasing preservatives (FRPs)
Balsam of Peru (<i>myroxylon pereirae</i> resin)	7%	Personal care products, spices, orange oil	Cheilitis	Cross-reactive with tomato, cinnamon, citrus, clove, spices
Lanolin	4.1%	Emollients, personal care products, nipple creams	Generalized in areas of emollient use	Should test with lanolin/wool alcohol
Propylene glycol	4%	Commonly used moisturizers, topical steroids and medicines, processed foods	Generalized skin irritation	Irritant reaction can occur
Benzophenones	1.7%	Sunscreens, Lip balms	Photo-exposed areas	Photo-testing may be needed
Parabens	0.6%	Sunscreens, personal care products	N/A	Uncommon allergen
Essential Oils	0.5-1.3%	"Natural products", toothpaste, gums, lozenges, diffusers	Airborne contact dermatitis	Patch test with patient's own product

Table 2

Topical Corticosteroid Potencies, Strengths, and Formulations Without Propylene Glycol

Class I: Superpotent/very high potency
Betamethasone dipropionate (ointment)
Diflorasone diacetate, 0.05% (ointment)
Flurandrenolide, 0.05% (Cordran Tape)
Desoximetasone, 0.25% (spray)
Class II: Potent/high potency
Betamethasone dipropionate, 0.05% (cream)
Desoximetasone, 0.25% (cream)
Desoximetasone, 0.05% (gel)
Diflorasone diacetate, 0.05% (ointment)
Halcinonide, 0.1% (ointment, solution)
Amcinonide 0.1% ointment
Class III: Upper midstrength/medium potency
Betamethasone valerate, 0.12% (Luxiq foam)
Betamethasone valerate, 0.1% (ointment)
Triamcinolone acetonide, 0.5% (ointment)
Class IV: Midstrength/medium potency
Desoximetasone, 0.05% (cream, ointment)
Fluocinolone acetonide, 0.03% (Synalar ointment)
Triamcinolone acetonide, 0.1% (Aristocort cream)
Triamcinolone acetonide, 0.1% ointment
Flurandrenolide, 0.05% (ointment)
Class V: Lower midstrength/lower-medium potency
Desonide, 0.05% (ointment, Tridesilon cream)
Hydrocortisone butyrate, 0.1% (cream, ointment)
Triamcinolone acetonide, 0.025% (ointment)
Flurandrenolide, 0.05% (Cordran lotion)
Class VI: Mild/low potency
Fluocinolone acetonide, 0.01% (oil)
Desonide, 0.05% (Verdeso foam)
Class VII: Least potent/lowest potency
Hydrocortisone 2.5% (Hytone ointment, Lacticare lotion, Nutricort lotion)
Hydrocortisone 1% (Hytone ointment, Cortizone 10 Maximum)

Table 3: Biologics used in treatment of Contact Dermatitis

Name	Mechanism of Action	Study Details	Study Results/ Immunological Changes
Dupilumab	Anti- IL4R [inhibits IL-4 and IL-13]	Retrospective Study¹ 64 adults with AD 17 with PT+ACD 14 with SACD 33 without ACD Retrospective Study² 7 adults with localized dermatitis refractory to Dupilumab were PT 6 adults underwent PT before Dupilumab Retrospective Study³ 15 adults with AD with hand dermatitis and/or childhood AD had PT performed Retrospective Study⁴ 48 adults with AD underwent PT Case Report⁵ 42 year old female with colophony allergy Case Report⁶ 54 year old surgeon with hand dermatitis refractory to Dupilumab was PT Case Report⁷ 44 year old male with nickel allergy to metal endovascular stents on MMF and Prednisone	After treatment, patients with PT+ACD and SACD had similar decrease in BSA, IGA, pruritus compared with those without ACD. All 7 patients had at least 1 + PT, with at least 1+ or stronger reaction 4 experienced complete resolution with Dupilumab and allergen avoidance, 3 continued to flare after treatment with allergen exposures BSA improvement of 70-100% in AD Recalcitrant facial dermatitis remained prevalent Only 10.4% of patch tests were “lost” after treatment Recall dermatitis delayed 24 hours after drug administration at PT site PT + for rubber accelerators while on Dupilumab, use of accelerator free gloves resolved hand dermatitis Dermatitis drastically improved on Dupilumab, MMF and Prednisone were weaned
Ustekinumab	Anti-IL-12 Anti-IL-23	Retrospective Study ⁷ 5 adults with	Brief clinical improvement (2 months) seen in only

		polysensitization to 3+ allergens without AD	1 patient, 2 patients developed skin infection
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Abbreviations: AD, atopic dermatitis; ACD, allergic contact dermatitis; BSA, body surface area; IGA, investigator's global assessment; MMF, mycophenolate mofetil; PT, patch test; PT+ACD, patch test confirmed allergic contact dermatitis; SACD, suspected allergic contact dermatitis

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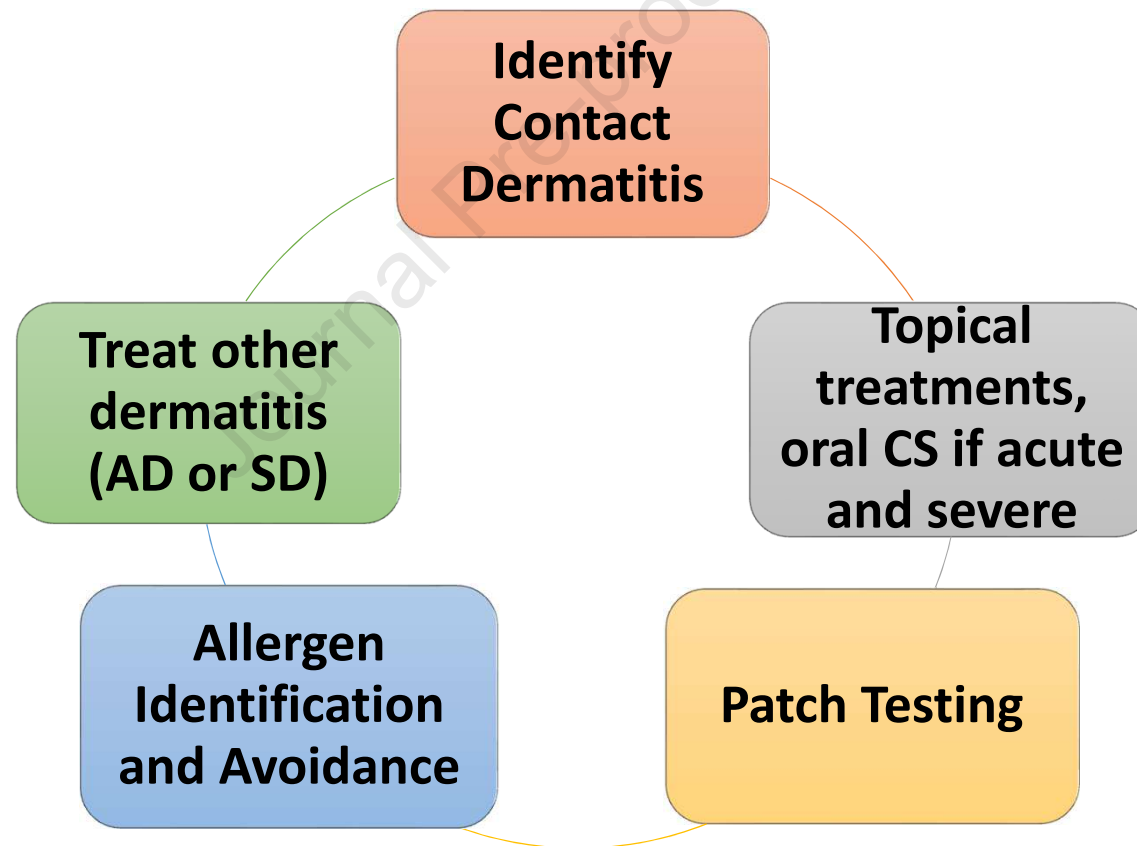


Figure 1. Budesonide 0.1% in petrolatum at 72 hours showing the edge effect and 7 days later showing a delayed positive test result.

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Figure 2: Management approach to Contact Dermatitis

Abbreviations: AD, atopic dermatitis; SD, stasis dermatitis; CS, corticosteroids



Key Messages:

- Nickel is the most common allergen, though many other sources of contact allergens are hidden in everyday products, such as preservatives and fragrances.
- In screening for contact allergies, it is important to inquire about wet work, or wet/dry cycles.
- The mechanisms of contact dermatitis are complex, and may involve different T-cell signaling pathways.
- Patch testing is required for diagnosis, and patch testing with patient's personal products is recommended.
- Management currently focuses on allergen avoidance, topical therapies, or corticosteroids; some biologics may be indicated for treatment.