

Patch Testing Interrupted: Virtual Patch Test Readings During the COVID-19 Pandemic

To the Editor:

Coronavirus disease 2019 (COVID-19) is a novel respiratory disease caused by severe acute respiratory syndrome coronavirus

2 (SARS-CoV-2). Emerging in China in December 2019, it has now spread to more than 200 countries.¹ The first case of COVID-19 in New Zealand was reported on February 28, 2020, and on March 25, 2020, New Zealand entered alert level 4 lockdown with border restrictions, banning of public congregation, and closure of all nonessential businesses and educational

TABLE 1. Summary of Patch Test Cases With Final Reading Performed by Telehealth

Case	Indication for Patch Testing	D2 Reading (In Person)	D5 Reading (Virtual)	Final Diagnosis	Outcome
15-y-old female adolescent	Hand dermatitis	Cobalt chloride +	Cobalt chloride + (irritant reaction not excluded)	Endogenous dermatitis	Clinical follow-up, patch test satisfactory
31-y-old woman	Eyelid dermatitis	Angry back	Nickel sulfate ++ (past relevance)	Endogenous dermatitis	Clinical follow-up, consider repeat testing
31-y-old man	Hand dermatitis	Nickel sulfate +, lanolin +	Nickel sulfate + (unknown relevance)	Psoriasiform dermatitis	Clinical follow-up, patch test satisfactory
27-y-old man	Cheilitis	Own toothpaste (10% in water), irritant	Methylprednisolone aceponate + (probable current relevance), hydroxyisohexyl 3-cyclohexene carboxaldehyde +/–, sodium benzoate +/– (strength of reaction and relevance not confirmed virtually)	Possible allergic contact dermatitis	Repeat patch test
52-y-old woman	Facial dermatitis	All negative	All negative	Endogenous dermatitis	Clinical follow-up, patch test satisfactory
61-y-old woman	Facial dermatitis	Colophonium +, <i>Myroxylon pereirae</i> +++, fragrance mix ++, tixocortol pivalate +++, hydroperoxides of linalool +, own sunscreen irritant (edge) reaction	<i>M. pereirae</i> +++, fragrance mix ++, tixocortol pivalate +++, isoeugenol ++, hydroperoxides of linalool ++, colophonium +/– (fragrance and steroid allergens probable current relevance)	Allergic contact dermatitis to fragrance and topical corticosteroid	Clinical follow-up, patch test satisfactory
69-y-old man	Anogenital dermatitis	All negative	Cobalt chloride + (irritant reaction not excluded)	Psoriasiform dermatitis	Clinical follow-up, patch test satisfactory
29-y-old woman	Cheilitis	All negative	All negative	Irritant contact dermatitis	Clinical follow-up, patch test satisfactory
53-y-old woman	Facial dermatitis	<i>M. pereirae</i> +/–	All negative	Irritant contact dermatitis and trigeminal trophic syndrome	Clinical follow-up, patch test satisfactory
56-y-old man	Hand dermatitis	Own glove irritant (edge) reaction	All negative	Psoriasiform dermatitis	Clinical follow-up, patch test satisfactory

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facilities in an attempt to reduce transmission of SARS-CoV-2.² On the advice of the New Zealand Dermatological Society, the majority of dermatological clinics closed from this date onward,

with the exception of acute assessments for life-threatening dermatological disease.

Before level 4 restrictions, 10 patients had commenced patch testing at our tertiary public hospital patch test clinic, with the application of patches and completion of day 2 (D2) reading. Because of the clinic closure, the final reading was attempted virtually, with clinical photographs taken by patients followed by a telehealth consultation. Patients were given instructions on how to take the photographs: an establishing shot of the back, close-ups of each panel, and any individual patch with color or textural change. If a confident post-patch test diagnosis could not be reached, or if there was a questionable reaction on photographs to a potentially important allergen, a repeat patch testing was recommended.

Characteristics and outcomes of cases are shown in Table 1. Irritant reactions were difficult to distinguish. For one case, the accuracy of the reading was felt to be ambiguous, and given a high pretest suspicion of allergic contact dermatitis, the test will need to be repeated. For a second case, we have recommended a follow-up with the referring dermatologist with the consideration of repeating patch testing if the condition persists. A woman due to return for patch test reading was subsequently classified as a COVID-19 "probable case" after developing symptoms of cough and fever with close contact to a confirmed case. Her symptoms developed on D4 of patch testing.

The virtual consultation presented a number of challenges. Medical practitioners need to be familiar with the telehealth equipment to be able to assist patients with troubleshooting. Videoconferencing platforms are unlikely to provide adequate resolution for readings; we used digital photography on patients' smartphones, and the photographs were generally of good to excellent quality. Oblique photographs of individual patches were helpful in deciphering induration and epidermal textural change; however, it was still difficult to decipher irritant from weak positive reactions. The inability to physically check the lists of ingredients in the patients' products made it more difficult to confidently ascertain the relevance. Virtual readings were the easiest when all patches were negative, particularly when the preferred prepatch test diagnosis was not allergic contact dermatitis.

Virtual readings are likely to have reduced accuracy and should not replace traditional patch testing methods. However, our clinics are already significantly underresourced with an average waiting time of more than 4 months for patch testing. Virtual readings were attempted to salvage any utility of the test given the extraordinary circumstances and were deemed satisfactory in 8 of the 10 cases. Patch testing will not resume in New Zealand until community transmission of COVID-19 ceases. Negative health outcomes due to indirect consequences of COVID-19 will occur, largely due to reprioritization of health resources. This includes delayed assessment of allergic contact dermatitis. Additional study comparing virtual with face-to-face readings is suggested to further explore the role of telehealth for patch testing.

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Psoriatic Plaques After Initiation of Dupilumab Therapy

To the Editor:

The long-term safety profile of dupilumab, a human monoclonal interleukin 4 (IL-4)/IL-13 inhibitor recently Food and Drug Administration approved to treat moderate to severe atopic dermatitis (AD), is lacking because of the relative infancy of this biologic agent.¹ This report describes 3 patients who developed erythematous plaques with micaceous scaling consistent with psoriasis within 1 year of dupilumab initiation (Fig. 1).

The first patient is a 32-year-old atopic woman with a diagnosis of hand dermatitis with biopsy-demonstrated subacute spongiotic dermatitis with eosinophils. One month after initiation of dupilumab, she developed significant itching and flaking of the scalp and pruritic red, raw patches along her bilateral inguinal folds and labia. On examination, several well-demarcated, bright red, erythematous plaques with micaceous scale were noted throughout the scalp, and sharply demarcated erythematous patches were noted in the bilateral inguinal folds, classic for psoriatic plaques. The second is a 67-year-old man with pruritic dermatitis of unclear etiology and biopsy-demonstrated spongiotic and lichenoid dermatitis with eosinophils. Two months after initiation of dupilumab, he reported significant improvement in itch (0/10) and rash; however, he developed a new pink scaly rash on his scalp consistent in appearance with psoriasis. The last patient is a 57-year-old woman with a long-standing history of severely pruritic dermatitis affecting the face and extremities, allergic contact dermatitis, and atopic eruption of pregnancy. She noticed drastic improvement in itch (0/10) and appearance in eczematous rash after only 2 weeks of dupilumab therapy. However, approximately 9 months after initiating treatment, she

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	Patient 1	Patient 2	Patient 3
Age (years)	32	67	57
Gender	Female	Male	Female
Time to plaque development (months)	1	2	9
Plaque location	Scalp, inguinal folds	Scalp	Scalp
Clinical Appearance			
Treatment	Topical corticosteroids	Topical corticosteroids	Topical corticosteroids

Figure 1. Demographics and summary of clinical course of 3 patients developing erythematous plaques with micaceous scaling consistent in appearance with psoriasis shortly after starting dupilumab treatment.

developed well-demarcated erythematous plaques with micaceous scaling on the frontal scalp, eyebrows, eyelids, and cheeks, clinically consistent with psoriasis.

There have recently been 4 other patients described who developed psoriatic plaques shortly after the initiation of dupilumab (2–18 months).^{2–4} These cases suggest novel development of psoriatic plaques associated with initiation of dupilumab even in individuals with no prior personal or family history of psoriasis. Timing between initiation and development of psoriatic plaques was relatively short, suggesting that occurrence of this phenomena may commonly occur within the first year of therapy. Interestingly, all 3 of our patients developed psoriatic plaques on their scalp. All lesions were clinically highly consistent with psoriasis, and as such, none of the plaques were biopsied, posing a potential limitation. In all patients, body surface area involvement was minimal, allowing for the treatment of lesions with topical steroids and the continuation of dupilumab therapy.

The AD and psoriasis are thought to exist as a T_H1 to T_H2 spectrum, with AD largely driven by the T_H2 pathway and psoriasis by T_H1 .⁵ Interleukin 4 has been postulated to have a regulatory role in the development of autoimmune disease.⁵ Our proposed theory is that inhibiting IL-4 with dupilumab perhaps overly skews the balance between the T_H1 and T_H2 responses in some individuals. It may also prevent IL-4 from serving its regulatory function in preventing the development of immune-related conditions. Given that 7 such cases have been described, prescribers should be aware of the potential for this phenomenon and the possible option of nevertheless continuing the medication in some cases.

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Contact Allergens in Beard Care Products

Over the past 2 decades, beards have become more common in the United States, and numerous companies have developed moisturizers to style and maintain a beard. These leave-on

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TABLE 1. Allergen Contents of Assessed Beard Care Products by Formulation

	Oil	Balm	Lotion
Total	31	20	8
Scents			
Fragrance	100.0%	100.0%	100.0%
Linalool	29.0%	5.0%	25.0%
Limonene	29.0%	15.0%	25.0%
Tea tree oil	—	15.0%	12.5%
Cinnamic acid	6.5%	10.0%	—
Preservatives			
Iodopropynyl butylcarbamate	—	10.0%	—
Sodium benzoate	—	10.0%	25.0%
Sorbic acid	—	5.0%	37.5%
Benzyl alcohol	3.2%	—	12.5%
Phenoxyethanol	—	20.0%	62.5%
Ethylhexylglycerin	—	15.0%	62.5%
Additives			
Tocopherol	51.6%	70.0%	62.5%
Decyl glucoside	—	—	25.0%
Propolis	6.5%	70.0%	12.5%
Propylene glycol	3.2%	—	12.5%
Cetylstearyl alcohol	—	20.0%	87.5%
Cocamidopropyl betaine	—	—	12.5%
Lanolin	—	45.0%	—
Sunscreen			
Benzyl salicylate	3.2%	—	—
Benzophenone-3	3.2%	—	—

Data shown as total number or percentage of products.

moisturizers come in several forms: oils, water-based lotions, or solid oil-based balms. These products are rubbed into the beard and underlying skin, and besides styling purposes, they may provide fragrance and function as antiseborrheics.¹ Despite their popularity, many beard care manufacturers do not participate in the Contact Allergen Management Program database. To help patch testing physicians recognize the allergenic potential and clinical relevance of these products, the contents of 59 beard moisturizers were assessed.

To identify products that are easily accessible, 3 popular stores that sell cosmetics—Walgreens, Target, and Ulta—were selected. All beard moisturizers on their Web sites were identified. Products were categorized as an oil, lotion, or balm. The ingredients listed on each product were assessed, and any allergens in the North American Contact Dermatitis Group or American Contact Dermatitis Society Core series were documented.

A total of 31 oils, 20 balms, and 8 lotions were assessed. Across all products, 20 allergens were present. All 59 products contained fragrance, and at least one quarter of oils and lotions contained linalool and/or limonene. Preservatives and emulsifiers were found primarily in lotions; the most common were phenoxyethanol (62.5%) and cetylstearyl alcohol (87.5%), respectively. Tocopherol was a common additive in oils (51.6%), balms (70.0%), and lotions (62.5%). Propolis (70.0%) and

lanolin (45.0%) were common in balms; notably, lanolin was not present in any of the oils or lotions. Two sunscreens—benzyl salicylate and benzophenone-3—were found in one oil but no other products. Among all products, the most common disclaimers were animal cruelty-free (40.7%), paraben-free (37.3%), sulfate-free (28.8%), and gluten-free (15.3%) (data not shown).

Although oils contained fewer allergens than lotions, this is at least partially due to differences in the need for preservatives. Furthermore, oils may not necessarily be less allergenic as many were made exclusively of essential oils. Two notable products—Beard Guyz Beard Oil and Jack Black Beard Oil—contained 27 and 17 distinct essential oils or plant-based fragrances, respectively. Given that beard oils are a leave-on product, the large number of fragrances may lead to sensitization. Another notable product, The Art of Shaving's Bergamot Neroli Oil, contains bergamot and bitter orange (neroli) oils. This is concerning given that both oils can cause a phytophotodermatitis.

A limitation of this investigation is that product manufacturers may not have listed all allergens. Although products may have contained numerous essential oils and fragrances, their exact concentrations are unknown. This is important because a threshold concentration is likely needed to induce sensitization or elicit a reaction in previously sensitized individuals.² Although

there are no reported cases of allergic contact dermatitis to beard moisturizers, it is plausible. Allergic contact dermatitis to para-phenylenediamine in beard dyes and methylisothiazolinone and diazolidinyl urea in scalp hair gel have been reported.^{3–5} Ultimately, patch testing physicians should be aware that many common allergens are present in beard care products, and the types of allergens vary between oils, balms, and lotions (Table 1).

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Ketotifen in Over-the-Counter Products Is a Contact Allergen

To the Editor:

We draw attention to 2 cases of periorbital dermatitis published in *Dermatitis* that identify ketotifen as the relevant contact allergen^{1,2} and report a third case herein.

We encountered a 55-year-old woman with a 2-year history of eye redness that started with bilateral eye irritation flaring in the spring and fall, later progressing to include an itchy rash around both eyes. She had been diagnosed with chronic allergic rhinoconjunctivitis and treated with subcutaneous allergen immunotherapy for about a decade. Her rhinitis symptoms were well controlled on immunotherapy, but the ocular problems persisted. She enjoyed gardening and had her nails manicured with nail polish or dip powder.

We conducted patch tests to Chemotechnique's North American Contact Dermatitis Group 80, cosmetic, and plant series and to

TABLE 1. Summary of Cases Reported of Ketotifen as a Contact Allergen

Author and Year of Publication	No. Patients	Country of Publication	Presenting Symptoms
Niizeki et al, ⁴ 1994	1	Japan	Periorbital dermatitis
Aoki et al, ³ 1997	6	Japan	Periorbital dermatitis
Smets et al, ⁵ 2017	1	Belgium	Chronic conjunctivitis
Aschenbeck and Warshaw, ¹ 2017	1	United States	Conjunctivitis and periorbital dermatitis
DeBord et al, ² 2019	1	United States	Conjunctivitis and periorbital dermatitis
Blackwell and Cruz, ⁶ 2020	1	United States	Conjunctivitis and periorbital dermatitis

her personal care products (olopatadine eye drops, Systane eye drops, Zaditor eye drops, makeup, sunscreen, and Vaseline). She reacted positively to methylidibromo glutaronitrile, neomycin sulfate, quaternium-15, and Zaditor eye drops.

Because ketotifen is the active ingredient in Zaditor eye drops, and we had recently reported the second case of periorbital dermatitis to ketotifen in the United States,² we suspected this medication as the cause of her dermatitis and had the patient stop it. Within 2 weeks, her ocular and periorbital symptoms completely resolved. We then provided additional counseling to avoid the other positive patch test allergens.

Ketotifen was first recognized as a contact sensitizer in a Japanese cohort published in 1997.³ Reported cases to date are summarized in Table 1. Ketotifen became available in the United States in 1999 and was sold as an over-the-counter medication starting in 2007.⁷ In the United States, ketotifen is currently only available in ophthalmic preparations: 1 generic and 7 branded.

Our experience raises the possibility that ketotifen in eye drops is an underrecognized cause of conjunctival and/or periorbital allergy. Such awareness is of particular importance because ketotifen is increasingly incorporated into products, including contact lenses that are in phase III trials,⁸ in addition to systemic preparations that are used outside the United States.

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Identifying Acrylates in Medical Adhesives

To the Editor:

Adhesives used in the medical settings consist of various acrylates and colophony derivatives, all of which are potential contact allergens.¹ Tape allergy is reported in 0.3% of patients.² Allergic contact dermatitis to medical adhesives can often be mistaken for skin infection especially in the perioperative setting leading to unnecessary antibiotic use. The exact compounds in medical adhesives remain unknown as manufacturers often withhold such information. Providers and patients resort to a trial and error process to identify safe options in the setting of adhesive allergy. The purpose of this qualitative screening study was to identify acrylates found in medical adhesives at a large tertiary care hospital.

Sixteen medical adhesives (7 medical/surgical tapes, 4 wound closure tapes, 2 hydrocolloid dressing, 1 transparent dressing, 1 transparent dressing with nonadherent pad, and 1 bandage) were extracted in acetone and analyzed using ultrahigh-performance liquid chromatographic (UHPLC) mass spectrometry (MS) (ThermoFisher Scientific Inc, Waltham, MA). One hundred milligrams of each adhesive was weighed and transferred into test vials containing 1 mL of acetone (1% wt/vol) and placed in a shaker for 1 hour. The extracts were then filtered and analyzed. An 8-microliter sample was injected into the UHPLC separated by a Symmetry Shield R18 analytical column (2.1 × 150 mm, 3.5 μm) at a flow rate of 0.3 mL/min using

0.1% formic acid in water as mobile phase A and 0.1% formic acid in acetonitrile as mobile phase B. The MS conditions were measured over 60 to 750 m/z under resolution power of 70,000. Colophony and (meth)acrylate-15 series (MA-1000) from Dormer-Chemotechnique (Vellinge, Sweden) served as standards (Table 1). Unfortunately, ethyl cyanoacrylate was not detected in our standard sample. Colophony, a distillate from trees of the *Pinus* species, is a common contact allergen used in adhesives of tapes, plasters, and dressings and various products.³ Colophony is composed of multiple resin acids. Abietic acid is the main component of colophony, which served as the target compound that we identified in the adhesive samples. A match in isotopic patterns and retention time between medical adhesive samples and standards were used to identify acrylates in each medical adhesive.

Fifteen of 16 medical adhesive samples had at least 1 detectable acrylate; 12 adhesives contained only 1 acrylate, 1 adhesive contained 2 different acrylates, and 2 adhesives contained 4 different acrylates (Table 2). Five acrylates were detected in the adhesive samples; triethyleneglycol dimethacrylate in 12 adhesives (68.8%), dimethylaminoethyl methacrylate in 4 adhesives (25%), 1,6-hexandiol diacrylate in 3 adhesives (18.8%), and tetrahydrofurfuryl methacrylate and tetraethyleneglycol dimethacrylate in 2 adhesives (12.5%). Abietic acid was detected in 5 adhesive samples (31.3%). Seven of 16 adhesives were listed as “hypoallergenic,” all of which contained acrylates and/or abietic acid.

This is the first study to date to systematically characterize acrylates in medical adhesives, which highlights the presence and prevalence of certain acrylates in medical adhesives. Various acrylates that were selected as standard reagents in this study, such as methyl methacrylate, 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, triethyleneglycol diacrylate, and ethylene glycol dimethacrylate, have been shown to detect more than 90% of acrylate sensitization in multiple studies.^{4,5} Interestingly, we found that adhesives from the same company do not contain the same acrylates. Furthermore, as demonstrated in this study, medical adhesives marketed as “hypoallergenic” may contain potential allergens such as colophony and acrylates, which can trigger ACD. It is worth noting that a limitation of this study was the inability to detect ethyl cyanoacrylate in our standard sample, which may be due to the difficulty of identifying this compound using UHPLC-MS. However, ethyl cyanoacrylate is a known compound used in skin glues and instant glues.⁶ Furthermore, we sampled only 16 medical adhesives because of cost. Results from this study provide important information on potential allergens that may be present in the medical adhesives examined, and extended patch testing can aid in diagnosis of ACD to medical adhesives. More comprehensive studies are needed to identify other potential allergens and their concentrations in all medical adhesives to guide clinical discussion and decision making for patients with medical adhesive allergy.

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TABLE 1. MS Values of Allergen Standards

(Meth)acrylate*	Rt, min	m/z (Exact)	m/z (Measured)	Mass Accuracy,† ppm	Medical Adhesive Samples, n (%)
Methyl methacrylate	6.67	101.06	101.06	2.8454	0 (0.0)
N-butyl methacrylate	9.76	143.11	143.11	−0.7538	0 (0.0)
2-Hydroxyethyl methacrylate	4.59	131.07	131.07	−0.9563	0 (0.0)
2-Hydroxypropyl methacrylate	5.34	145.09	145.08	−1.0363	0 (0.0)
Ethyleneglycol dimethacrylate	8.74	199.10	199.10	−0.5034	0 (0.0)
Triethyleneglycol dimethacrylate	8.38	287.15	287.15	−1.5392	12 (68.8)
1,4-Butanediol dimethacrylate	9.65	227.13	227.13	−1.7363	0 (0.0)
Urethane dimethacrylate	10.02	485.29	485.29	−0.2596	0 (0.0)
Bisphenol A dimethacrylate	11.85	365.17	365.17	−1.5778	0 (0.0)
Bisphenol A glycerolate dimethacrylate	10.16	513.25	513.25	−0.9494	0 (0.0)
1,6-Hexandiol diacrylate	9.38	227.13	227.13	−1.3332	3 (18.8)
Tetrahydrofurfuryl methacrylate	7.12	171.10	171.10	−1.4707	2 (12.5)
Tetraethyleneglycol dimethacrylate	8.23	331.18	331.17	−1.7195	2 (12.5)
N,N-dimethylaminoethyl methacrylate	1.35	158.12	158.12	−2.1628	4 (25.0)
Colophony					
Abietic acid	13.11	303.23	303.23	−2.4746	5 (31.3)

*Ethyl cyanoacrylate was not detected among the allergen standards.

†Targets were considered detected when mass accuracy was within ± 5 ppm and if there was a match in isotopic patterns between the observed and theoretical and a match in retention times between standards and medical adhesive samples.

min indicates minutes; ppm, parts per million; Rt, retention time;

TABLE 2. Meth(acrylate) and Colophony (Abietic Acid) Content in Medical Adhesives

Product	Adhesive Category	Hypoallergenic (Yes/No)	Acrylate Content
3M Durapore 1538-2	Medical tape, surgical tape	Yes	Tetrahydrofurfuryl methacrylate Abietic acid–colophony
3M Medipore Soft Cloth 2962S	Medical tape, surgical tape	Yes	Triethyleneglycol dimethacrylate
3M Micropore 1533-1	Medical tape, surgical tape	Yes	Triethyleneglycol dimethacrylate 1,6-Hexandiol diacrylate Tetraethyleneglycol dimethacrylate N,N-dimethylaminoethyl methacrylate
3M Transpore 1527-1	Medical tape, surgical tape	No	N,N-dimethylaminoethyl methacrylate Abietic acid–colophony
3M Transpore 1527S-1	Medical tape, surgical tape	No	Triethyleneglycol dimethacrylate 1,6-Hexandiol diacrylate
3M Transpore 1534S-1	Medical tape, surgical tape	No	Triethyleneglycol dimethacrylate 1,6-Hexandiol diacrylate Tetrahydrofurfuryl methacrylate N,N-dimethylaminoethyl methacrylate
Covidien Kendall Standard Porous Tape 3615C	Medical tape, surgical tape	No	Triethyleneglycol dimethacrylate
3M Steri-Strip R1542	Skin closure	Yes	Tetraethyleneglycol dimethacrylate
3M Steri-Strip R1546	Skin closure	Yes	Triethyleneglycol dimethacrylate
3M Steri-Strip B1550	Skin closure	Yes	Triethyleneglycol dimethacrylate
3M Steri-Strip B1551	Skin closure	Yes	Triethyleneglycol dimethacrylate
3M Tegaderm film 1642 W	Transparent dressing	No	Triethyleneglycol dimethacrylate Abietic acid–colophony
3M Tegaderm + Pad 3582	Transparent dressing with nonadherent pad	No	None determined
DuoDerm CGF 187660	Hydrocolloid dressing	No	Triethyleneglycol dimethacrylate Abietic acid–colophony
Allevyn Life foam dressing 66801068	Hydrocolloid dressing	No	Triethyleneglycol dimethacrylate
Coverlet Adhesive Dressing	Bandage	No	N,N-dimethylaminoethyl methacrylate Abietic acid–colophony

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Clogs Are a Fashionable Option in Cases of Shoe Contact Dermatitis

To the Editor:

Allergic contact dermatitis (ACD) to footwear most commonly presents as bilateral, symmetric dermatitis of the dorsal feet as a result of sustained contact with the upper shoe¹; the plantar

surface may also be involved. The occlusive/sweaty environment created by shoes is a particularly high risk for enhancing the absorption of potential allergens.² Among chemicals used in the shoe manufacturing process, rubber ingredients, adhesives, dyes, and leather additives (including potassium dichromate and octylisothiazolinone³) are known culprits of shoe ACD.^{4,5} Allergen avoidance can be extremely challenging, as these materials are ubiquitous shoe components. Anecdotally, many patients report frustration with a lack of safe shoe alternatives; moreover, shoes free of the previously mentioned materials are often deemed unbecoming. In seeking additional, fashionable options for our patients with ACD to shoes, we sought to determine the presence of common contact allergens in clogs and whether they could represent a suitable alternative for individuals with shoe dermatitis.

An online search was conducted to determine major clog brands. Information was obtained from the manufacturer's website and from discussion with company representatives. Specifically, the presence and type of rubber, adhesives, wood, leather, and dyes were investigated.

Information was obtained from 8 clog companies (5 international and 3 United States; Table 1). The majority used alder wood and/or limewood for the clog base. The clog sole (no direct skin contact) was made of rubber (n = 4), polyurethane (n = 3), or cork and latex (n = 1). Six companies affirmed the use of vegetable tannins in their natural leather clogs; colored leather was often chrome tanned or consisted of an unknown dye composite mixture. Adhesives were typically used in gluing the wooden base to the rubber/polyurethane sole (no direct skin contact; Fig. 1) and in small leather heel pad protectors (potential skin contact; Fig. 2); adhesive brand/ingredients were mostly unknown. Nickel-free staple and buckle options were available for individuals with concomitant nickel allergy. In addition, custom-made clogs were offered by 3 companies. Multiple designs from strappy high-heeled dress shoes to enclosed flats were available. Cost varied widely based on the company and style and ranged from US \$50 to \$350.

Overall, clogs seem to be an excellent shoe alternative for patients with rubber allergy; direct foot contact with rubber was absent among all clog types, although rubber-sensitive individuals should exercise caution when handling rubber soles. Additional options for rubber-allergic patients include purchasing either clogs with a polyurethane sole or those with a wooden base only. Chrome-tanned leather was used by 3 companies; however, natural, vegetable-tanned leather is readily available for patients with chromate sensitivity. Although specific adhesives were unknown or undisclosed by most companies, adhesives can be avoided by ordering clogs without a heel pad or removing the pad and sanding the wooden footbed. Importantly, custom-made clogs free of particular chemicals can be ordered for individuals desiring assurance of allergen avoidance.

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TABLE 1. Information Obtained From US and International Clog Companies

	Wood	Rubber	Adhesives	Dye	Cost*	Other
Birkenstock birkenstock.com/us (Neustadt, Germany)	No wood (cork/latex footbed)	Latex used in footbed; no rubber present in sole (ethylene vinyl acetate sole) Soles do not contain mercaptobenzothiazole	Water-soluble and solvent-free adhesive used in attaching sole to footbed (no direct skin contact) Adhesives are free of abitol, abietic acid, colophony, and <i>P-tert</i> -butylphenol formaldehyde resin	Vegetable tanned; some leather is chrome-tanned	\$	Offers vegan clog alternatives; staples and buckles are nickel-free
Lotta lottafromstockholm.co.uk/ clogs.html (Stockholm, Sweden)	Alderwood	Rubber soles (no direct skin contact)	Present in heel pad (potential skin contact) and on wooden base (no direct skin contact) Leather is stapled	Vegetable tanned; chrome-free	\$	
Multnomah Leather Shop multnomahleather.com (Portland, OR)	Alderwood	Vinyl and rubber soles (no direct skin contact)	Rubber cement used on wooden base (no direct skin contact) Water-based polyurethane adhesive used on upper leather (potential skin contact)	Natural leather—vegetable tanned Colored leather—chrome-tanned	\$	Offers custom clogs; uses a wooden midsole such that feet are isolated from cemented outsole
No. 6 no6store.com/collections/ shoes-no-6-clogs (New York, NY)	Lacquered wood ("proprietary information")	Polyurethane soles (no direct skin contact)	Leather is nailed (steel) Heel pads attached with an adhesive (potential skin contact)	Chrome-tanned leather	\$\$\$	Offers custom clogs
Sandgrens sandgrensclogs.com (Småland, Sweden)	Limewood or Spanish pine	Thermoplastic rubber soles (no direct skin contact)	Leather is stapled Present in heel pad (potential skin contact) and on wooden base (no direct skin contact) Leather is stapled	Natural leather—vegetable tanned and nubuck Colored leather—dyed (chrome-free)	\$	Staples and buckles are nickel-free
Sven Clogs svenclogs.com/ (Chicago City, Minnesota)	Limewood or poplar	Bendable base—polyurethane sole (no direct skin contact) Nonbendable base—wood only	Present in heel pad (potential skin contact) and on wooden base (no direct skin contact) Leather is stapled pad	Colored leather is predyed (unknown dye)	\$	Offers custom clogs

TABLE 1. (Continued)

	Wood	Rubber	Adhesives	Dye	Cost*	Other
Swedish Hasbeens swedishhasbeens.com (Stockholm, Sweden)	Alderwood or linewood	Rubber soles (no direct skin contact)	Present in heel pad (potential skin contact) and on wooden base (no direct skin contact) Leather is stapled	Natural leather—vegetable tanned; chrome-free Colored leather—vegetable tanned with small amount of chrome (chrome-free per EU regulations)	\$\$	
Troentorp troentorpsclogs.com (Båstad, Sweden)	Alderwood	"Ideal" sole—polyurethane (no direct skin contact) "Original" sole and mid sole—wood only	Present in heel pad (potential skin contact) and on wooden base (no direct skin contact) In cases where leather is lined, adhesives are used to attach liner to leather (potential skin contact) Leather is nailed	Natural leather: vegetable tanned, suede, nubuck Colored leather: pull-up (aniline dyes)	\$	Many chrome-free options are available

*Average price estimates for standard clogs (not including clog boots), as per January 2020 manufacturer Web sites: \$, US \$50–\$150; \$\$, US \$150–\$250; and \$\$\$, US \$250–\$350.



Figure 1. Example of a rubber sole (no direct skin contact) glued onto the bottom of a wooden sole.



Figure 2. Example of a leather heel pad (potential skin contact) glued onto the footbed.

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Defining Topical Corticosteroids by Allergenicity and Cross-Reactivity for the Contact Allergen Management Program

To the Editor:

Allergy to topical corticosteroids is not uncommon, with approximately 4% of patch-tested patients affected.¹ The allergenic potential of corticosteroids is influenced by their biochemical structure; in general, substitutions on C₁₆, C₁₇, and C₂₁ are considered

the most significant. Methylation or halogenation of C₁₆ reduces allergenicity by stabilizing the corticosteroid structure, hindering hydrolysis of C₂₁, and preventing reactions with arginine (the by-products of which result in sensitization).^{2,3} Based on structural characteristics, corticosteroids have been categorized into 4 groups (with 1 subgroup): groups A, B, C, and D1/D2 (Table 1).² Although this system creates a framework for thinking about the allergenicity and cross-reactivity of corticosteroids within a group, exceptions exist, with cross-reactivity between groups being frequently reported.^{2,3} In general, Contact Allergen Management Program (CAMP) considers allergens to cross-react if concurrent reactions occur at a frequency higher than 10%. In this article, the CAMP Cross-Reactor Committee describes the framework for how CAMP categorizes topical corticosteroids based on cross-reactivity.

Corticosteroid groups A, B, and D2 consist entirely of non-C₁₆-methylated corticosteroids, creating a potential for cross-reactivity (Table 1).^{1,2,5} Among this group, allergies are most frequently observed to groups B and D2 corticosteroids and to a lesser extent group A corticosteroids.⁵ In a study by Pratt et al¹ of

TABLE 1. Cross-Reactivity Patterns Across the 5 Different Recognized Groups of Corticosteroids

	Grouping of Topical Corticosteroids*				
	A	B	D2	C	D1
	Hydrocortisone Type	Triamcinolone Type	Methylprednisolone Aceponate Type	Betamethasone Type	Betamethasone Dipropionate Type
Key structural characteristics	No substitutions present on the D ring, [†] but there is a short-chain ester or thioester present on C ₂₁	<i>cis</i> -Ketal or <i>cis</i> -diol additions on C ₁₆ /C ₁₇	C ₁₆ is nonmethylated and nonhalogenated, a long-chain ester on C ₁₇ , and a possible side chain present on C ₂₁ .	Methylated C ₁₆ and halogenated C ₆ or C ₉	Methylated C ₁₆ and a long-chain ester on C ₁₇ /C ₂₁
Screening allergen	Tixocortol-21-pivalate	Triamcinolone acetonide Budesonide	Hydrocortisone-17-butyrate	Desoximetasone	Clobetasol-17-propionate
Nonscreening allergens	Cortisone acetate	Amcinonide	Hydrocortisone valerate	Betamethasone ± disodium phosphate	Alclometasone dipropionate
	Fludrocortisone acetate	Desonide	Prednicarbate	Dexamethasone	Betamethasone dipropionate
	Fluorometholone	Flunisolide		Difluocortolone pivalate	Betamethasone valerate
	Hydrocortisone	Fluocinolone ± acetonide			Diflorasone diacetate
	Methylprednisolone ± acetate	Halcinonide			Fluticasone propionate
	6-α-Methylprednisolone acetate	Triamcinolone ± hexacetonide			Halobetasol propionate
	Prednisolone ± acetate				Mometasone furoate

This table illustrates cross-reactivity patterns across the 5 different recognized groups of corticosteroids.⁴ Groups A, B, and D2 are considered to cross-react, whereas C and D1 have minimal cross-reactivity below the 10% threshold used by CAMP.

*Information adapted from Fisher's *Contact Dermatitis*, 7th ed.⁴

[†]The D ring refers to the cyclopentane ring consisting of C13–C17.

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156 patients with reactions to group B, 18.6% also reacted to group A, and 23.7% reacted to group D2. Of 77 patients with reactions to group D2, 27.3% reacted to group A, and 48.1% reacted to group

B corticosteroids.¹ Based on reports of frequent cross-reactivity and similarities in biochemical structure, a reaction to a group A, B, or D2 corticosteroid will default to all 3 groups of corticosteroids being eliminated for the patient. The prescribing physician can override this if needed with advanced CAMP functionality.

Groups C and D1 corticosteroids have several features resulting in increased molecular stability, decreased skin sensitization, and decreased cross-reactivity between groups (Table 1). Groups C and D1 corticosteroids are considered to be significantly less allergenic than non-C₁₆-methylated corticosteroids and thus often preferred in the setting of presumed corticosteroid allergy.⁵ Although there is some literature to suggest possible cross-reactivity of group C with group D1, we hold that these 2 groups should not be considered to cross-react.^{1,3} In general, the predictability of corticosteroid cross-reactivity is significantly overestimated and often based on results of screening allergens rather than comprehensive testing of large corticosteroid series; furthermore, in our clinical experience, any reactions between group C and D1 corticosteroids are not greater than the 10% CAMP threshold. Accordingly, if a group C or D1 corticosteroid is selected, CAMP does not eliminate any other corticosteroid groups.

In summary, corticosteroids have traditionally been categorized based on their allergenic potential into groups A, B, C, and D1/D2. If a patient is allergic to any non-C₁₆-methylated corticosteroid, CAMP will also eliminate other non-C₁₆-methylated corticosteroids. Written another way, a reaction to a steroid within group A, B, or D2 will result in all 3 groups of corticosteroids being eliminated for the patient. For C₁₆-methylated steroids (groups C and D1), which do not have evidence of cross-reactivity exceeding the 10% threshold used by CAMP, cross-reactors are not automatically included by CAMP.

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Patch Testing: Analysis of Internet-based Education Material

To the Editor:

Patients increasingly rely on the Internet to expand health care knowledge, and self-gathered information may impact patient decisions.^{1–3} Because of the active role patients must take in the patch testing procedure, patient education is an essential component of care.³ The quality of online patch testing information readily available to patients utilizing common search engines was evaluated.

The top 50 search results were generated from Google, Yahoo!, and Bing using the term “patch testing,” excluding

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TABLE 1. Authorship and Content Analysis of Patch Testing Web Sites

Parameter	Unique Web Sites, n (%)	HONcode (n = 19)	P*
Authorship (n = 90)			
Academic (hospital or university)	15 (16.7)	4	0.5121
Private physician/clinic	13 (14.4)	0	0.0624
Manufacturer/industry	11 (12.2)	0	0.1113
Publication by physician	13 (14.4)	7	0.0050
Medical association/society	4 (4.4)	1	1.0000
Commercial, news, blog	18 (20.0)	2	0.3416
Other	16 (17.8)	5	0.3148
Content analysis (n = 67)			
Purpose	64 (95.5)	19	0.5526
Benefit	22 (32.8)	5	0.5714
Description of procedure			
No description	6 (9.0)	1	0.6666
Uninformative (score 1–2)	15 (22.4)	5	0.7467
Brief mention (score 3–4)	33 (49.3)	5	0.0291
Thorough (score 5–6)	13 (19.4)	8	0.0059
Special considerations			
Any special consideration	45 (67.2)	14	0.5714
0–1 Mention	31 (46.3)	7	0.4187
2–3 Mentions	26 (38.8)	7	1.0000
4–5 Mentions	10 (14.9)	5	0.1318
Risks			
Any risk	26 (38.8)	10	0.1715
Rash at application site	24 (35.8)	8	0.5763
Reaction to tape	13 (19.4)	5	0.4940
Pigmentary changes	11 (16.4)	4	0.4923
Rash reactivation/recall	11 (16.4)	5	0.2702
Sensitization to allergens	10 (14.9)	4	0.4521
Acute allergic reaction	8 (11.9)	4	0.2094
“Angry back”	7 (10.4)	5	0.0166
Appointment	24 (35.8)	2	0.0098
References	14 (20.9)	8	0.0162

Note that authorship was of all 90 unique sites queried. Content analysis was only of included relevant sites, which included 67 unique sites.

*Comparison of content between HONcode-certified sites and noncertified sites, made using the Fisher exact test. Bolded P values indicate statistical significance.

duplicate sites. Authorship was categorized. Relevancy of sites was determined for inclusion in content analysis. Relevant web sites provided information pertaining to the clinical patch testing procedure. A cross-reference to Health on the Net Foundation (HON), a certification body, was performed using a web browser toolbar extension.⁴ The purpose was reported if a site stated that patch testing is a procedure used to diagnose allergic contact dermatitis or determine relevant allergens. The benefit of patch testing was reported if a site stated that patch testing results are used to develop an avoidance plan and prevent the recurrence of rash. The description of procedure evaluated 6 criteria: description of allergen selection, how

patch testing is performed (allergens taped to back), visits and readings required, reading interpretations, statement of difference between prick testing, and use of photographs or videos. There were 5 special considerations: testing only on areas of clear skin, UV avoidance during testing, keeping patches dry during testing, no immunosuppressive drugs, and avoidance of hot and sweaty activities.

Of all sites queried (150 sites), there were 90 unique sites, 19 of which were HONcode certified (21% [19/90]). Only 67 unique sites met the inclusion criteria for content analysis, including all HONcode-certified sites (28.4% [19/67]). Of the sites excluded, 57% (13/23) were authored by commercial advertisements, brands, and blogs that discussed home patch testing to products for irritation rather than for diagnosis of allergy. The results of parameters analyzed are shown in Table 1.

Authorship by academic institutions and societies was limited, constituting only 17% and 4% of authorships, respectively. Purpose of patch testing was reported in 95.5% (64/67) of sites. Patch testing benefit and risks were mentioned only in 32.8% (22/67) and 38.8% (26/67) of sites, respectively. A total of 81% (54/67) of web sites provided no mention, uninformative, or brief description of the patch testing procedure. At least 1 special consideration was mentioned in 67% (45/67) of sites. Only 21% (14/67) of sites cited peer-reviewed literature.

In summary, this is the first study to analyze the quality of patient information online regarding patch testing, and results show that reliable and quality information online is limited and not easily accessible. Improved and comprehensive online patient information is needed.

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Severe Adult Atopic Dermatitis: Clinical Challenges

To the Editor:

In recent years, better understanding of the pathogenesis of atopic dermatitis (AD) has allowed improvement of treatment strategies with emerging therapeutic options. Currently, dupilumab, a monoclonal antibody that selectively inhibits interleukin 4 (IL-4) and IL-13, is the only biological drug authorized for the treatment of severe adult AD. This emerging and innovative therapy has been authorized in Italy since September 2018. In our experience, we have faced some clinical challenges that should be discussed.

The formulation of a correct diagnosis is a critical issue in these patients because of the extreme clinical heterogeneity of adult AD, which includes atypical clinical variants such as chronic hand eczema, nummular eczema, and atopic prurigo. In addition to the extremely heterogeneous clinical picture, AD can present with various grades of disease severity, including acute and chronic phases. Dupilumab prescription in Italy is subjected to Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]) monitoring, which imposes as a fundamental requirement the presence of an Eczema Area and Severity Index (EASI) equal to or greater than 24. The AIFA is the national authority responsible for drug regulation in Italy. It is a public body operating autonomously, transparently, under the direction of the Ministry of Health and under the vigilance of the Ministry of Health and the Ministry of Economy.

In everyday practice, it is easy to find clinical pictures, which, although not excessively extensive, do, however, involve visible areas (such as face and hands) and/or genitals and therefore have a negative impact on patient quality of life but still do not reach an adequate EASI for prescription purposes. Moreover, according to AIFA cost-effectiveness criteria, if the patient has not achieved an EASI 50 at the time of mandatory re-evaluation at 16 weeks, it is not possible to continue with the therapy, even if the Dermatology Life Quality Index and the pruritus Numerical Rating Scale (NRS) dramatically improved (Table 1). This limitation puts the dermatologist in a difficult position concerning therapeutic management, especially with patients who can be considered a late or partial responder.¹ Based on our clinical experience, in such cases it may be necessary, after having verified the certainty of the diagnosis, to add topical calcineurin inhibitors or topical or oral corticosteroids with dupilumab before considering patients as nonresponders.

TABLE 1. Variation of EASI, DLQI and NRS Pruritus Score

Patients	EASI			DLQI			NRS Pruritus		
	T0	T16	Δ%	T0	T16	Δ%	T0	T16	Δ%
1	28	14	50%	28	10	64%	8	1	88%
2	24	10	58%	24	6	75%	9	3	67%
3	32	16	50%	30	10	67%	10	3	70%
4	24	12	50%	30	12	60%	10	4	60%
5	24	11	54%	30	13	57%	9	2	78%
6	24	12	50%	14	6	57%	8	2	75%
7	36	18	50%	23	14	39%	8	2	75%
8	29	14	52%	12	8	33%	8	0	100%

EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; NRS, Numerical Rating Scale.

In our opinion, patient reassessment can be postponed for 2 additional months (week 24) and in addition to EASI, pruritus NRS, sleep NRS, and Dermatology Life Quality Index should also be administered and evaluated. The combined use of these scores could offer a broader overview of the impact of AD on quality of life, integrating skin examination with health as perceived by the patient, representing a valuable support in the process of choosing therapy and response to treatment. In addition, the patient management could also evaluate the impact of AD on families, the socioeconomic impact, the direct and indirect costs, and the loss of productivity at work.²

Recent studies have shown that, in patients treated with dupilumab, after 16 weeks of treatment the gene expression profile of lesional skin had shifted toward that of nonlesional skin with an important reduction in the gene expression of the related T-helper 2 (T_H2) cytokines. In particular, dupilumab significantly suppressed systemic type 2 inflammatory biomarkers in serum, including the type 2–driven chemokines CCL17 and CCL18, periostin, and total and allergen-specific immunoglobulin E. This phenomenon was accompanied not only by a reduction in the expression of the genes involved in the T_H17/T_H22 pathways, but also by an up-regulation in the expression of barrier lipids (eg, filaggrin, loricrin, claudin, and fatty acids) and significant reduction in epidermal hyperplasia.³ At week 36 of SOLO-CONTINUE, long-term response was consistently maintained with dupilumab every 2 weeks, including maintenance of improvement in AD signs, symptoms, and quality of life.⁴ These results support that dupilumab therapy has the potential, over time, to change the history of this disease. For this reason, relying on the achievement of EASI 50 at 16 weeks as the sole measurement of clinical objectivity limits a comprehensive evaluation of the efficacy of the drug, denying the patient a therapeutic opportunity that could be valid.

Today, the management of these complex circumstances is a challenge for dermatologists, and an agreement about follow-up, duration of treatment, and patient evaluation criteria shared by

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all the Dermatologic Therapy Units of Italy is mandatory to review the criteria proposed by AIFA.

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