

Allergic Contact Dermatitis of the Anogenital Region in Men and Women

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Objectives: Allergic contact dermatitis is an uncommon but important cause of skin disease in the anogenital region. Relevant allergens are described in women and less commonly in men. The aim of this study was to describe outcomes of patch testing in men and women presenting with anogenital dermatoses.

Materials and Methods: Cases patch tested for anogenital conditions at 2 patch test clinics in Sydney, Australia, from 2002 to 2017 were reviewed. Positive and relevant patch test reactions were recorded.

Results: Thirty-seven women and 27 men were included. Dermatitis was the most common diagnosis, followed by psoriasis and lichen sclerosus. Thirty percent had a final diagnosis of allergic contact dermatitis. The most frequent relevant allergens were fragrance mix I (9%), patients own products (9%), *Myroxylon pereirae* (8%), cocamidopropyl betaine (3%), and benzocaine (3%).

Conclusions: The top positive and relevant allergens seen were in concordance with other reports from Australia and the rest of the world. Fragrances and medicaments are common allergens, and it is recommended that products used on anogenital skin be fragrance free. Testing patients own products is imperative.

Key Words: patch testing, allergic contact dermatitis, genital dermatitis, contact eczema, fragrance

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The moist and occluded nature of genital and perianal skin increases susceptibility to contact dermatitis. Allergic contact dermatitis (ACD) is much less common than irritant contact dermatitis¹; however, if missed, it may lead to chronic disease. Reported allergens include topical medications (including anesthetics and corticosteroids), preservatives, and fragrance.^{2–5} There are case reports of vulval ACD to sanitary pads.^{6,7} Rubber in condoms may cause immediate reactions, because of type 1 hypersensitivity to latex or delayed-type reactions most often to rubber accelerators present in both latex and synthetic rubber. Seminal fluid can cause immediate hypersensitivity and contact urticaria.⁸ Allergic hypersensitivity to *Candida albicans* has been associated with vulvodynia with increased positivity on patch testing to ultraviolet-killed *C. albicans* compared with patients without vulvodynia.⁹

Allergic contact dermatitis is mediated by delayed-type hypersensitivity to a specific allergen after previous topical exposure results in sensitization. Mucosal surfaces are more permeable than keratinized epithelium that may increase the potential for sensitization; however, immune mechanisms of both oral and vaginal mucosa may promote tolerance over sensitization.^{10,11}

The criterion standard diagnostic test for detecting contact allergy caused by delayed-type hypersensitivity is patch testing, which is performed by applying allergens on the patient's back. Positive results are then classified as being of past or current relevance to the patient's presenting problem. A current relevant allergen is defined as an allergen with current skin contact in the distribution of affected skin. Testing is performed with a baseline series; a group of the most relevant allergens in the given population, with additional specialized series (e.g., fragrances, steroids, preservatives) added depending on the clinical presentation. Patients' own products are usually added in addition to series allergens. Results of patch testing for genital conditions are perhaps better characterized in women; however, after patch testing, men may be more likely to have a final diagnosis of contact dermatitis.² The objective of this study was to document outcomes of patch testing in men and women with dermatoses of the anogenital region in an Australian population.

METHODS

A 15-year retrospective review was performed for patient's patch tested at 2 private contact dermatitis clinics in Sydney, Australia. Ethics approval was granted by The University of Sydney Human Research Ethics Committee. Patients were referred for patch testing by specialists or primary care physicians. Testing was performed using Chemotechnique IQ Ultra chambers. Patches were removed on day 2 and readings performed on days 2, 4, and 7 were graded in accordance with International Contact Dermatitis Research Group guidelines.

Data were collected on series tested, pre- and post-patch test diagnosis (the primary diagnosis was recorded where multiple diagnoses present), positive, and relevant reactions. Statistical analysis was performed using SPSS Statistics Version 23 (IBM Corporation, 2015, Armonk, NY). Comparisons between men and women were made using Fisher exact test. Differences between means were calculated using a 2-sample *t* test. The significance level was set at α value of 0.05.

RESULTS

Of 3,460 patients patch tested over the study period, 64 were referred with anogenital dermatoses (2%). There were 37 women (58%) with a mean (SD) age of 51 (17.9) years and 27 men (42%) with a mean (SD) age of 47 (17.5) years. Fifteen (23%) of the 64 were considered atopic. Compared with the total population patch tested during this period, the group with anogenital skin disease had a lower proportion of females (56% vs. 67%) and an older mean age (49 vs. 44 years). The most common pre-patch test diagnosis was dermatitis (including atopic, allergic, and irritant contact dermatitis) followed by psoriasis and lichen sclerosus.

In addition to the baseline series, specialized series tested included antimicrobials and preservatives ($n = 37$), corticosteroids ($n = 36$), fungicides ($n = 14$), and perfumes/flavors ($n = 9$). Thirty-four patients (53%) had at least one positive reaction and 19 (30%) had at least one relevant reaction and were diagnosed with ACD. The most commonly positive allergens were nickel ($n = 10$), fragrance mix I ($n = 8$), *Myroxylon pereirae* ($n = 8$), dodecyl gallate ($n = 6$), and cobalt chloride ($n = 6$). The most

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TABLE 1. Positive Patch Test Reactions in Men and Women With Anogenital Dermatoses (N = 64)

Allergen	Men (n = 27), n (%)	Women (n = 37), n (%)	Total (%)	% relevant/positive
Nickel sulfate	2 (7.4)	8 (21.6)	10 (15.6)	0
Fragrance mix I	2 (7.4)	6 (16.2)	8 (12.5)	75
<i>Myroxylon pereirae</i>	2 (7.4)	6 (16.2)	8 (12.5)	63
Patients own product	3 (11.1)	3 (8.1)	6 (9.4)	67
Dodecyl gallate	2 (7.4)	4 (10.8)	6 (9.4)	17
Cobalt chloride	1 (3.7)	5 (13.5)	6 (9.4)	0
Benzocaine	2 (7.4)	1 (2.7)	3 (4.7)	67
Cocamidopropyl betaine	2 (7.4)	1 (2.7)	3 (4.7)	67
p-Phenylenediamine	0 (0)	3 (8.1)	3 (4.7)	0
Thiomersal	0 (0)	3 (8.1)	3 (4.7)	0
Pimecrolimus 1% cream	0 (0)	2 (5.4)	2 (3.1)	100
Benzalkonium chloride	1 (3.7)	1 (2.7)	2 (3.1)	50
Diazolidinyl urea	1 (3.7)	1 (2.7)	2 (3.1)	50
Methyldibromo glutaronitrile	1 (3.7)	1 (2.7)	2 (3.1)	50
Hydrocortisone 1%, clotrimazole 1% cream	1 (3.7)	1 (2.7)	2 (3.1)	50
Sodium metabisulfate	1 (3.7)	1 (2.7)	2 (3.1)	50
Imidazolidinyl urea	1 (3.7)	1 (2.7)	2 (3.1)	0
Potassium dichromate	1 (3.7)	1 (2.7)	2 (3.1)	0
Hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine	0 (0)	1 (2.7)	1 (1.6)	100
Butyl-4-hydrobenzoate	0 (0)	1 (2.7)	1 (1.6)	100
Coconut diethanolamide	0 (0)	1 (2.7)	1 (1.6)	100
Formaldehyde	0 (0)	1 (2.7)	1 (1.6)	100
MCI/MI (Kathon CG)	1 (3.7)	0 (0)	1 (1.6)	100
Quaternium-15	0 (0)	1 (2.7)	1 (1.6)	100
Tolnaftate 1% cream (Tineafax)	0 (0)	1 (2.7)	1 (1.6)	100
Wool alcohols	1 (3.7)	0 (0)	1 (1.6)	100
4-tert-Butylphenol formaldehyde resin	0 (0)	1 (2.7)	1 (1.6)	0
Benzoyl peroxide	0 (0)	1 (2.7)	1 (1.6)	0
Chloroacetamide	1 (3.7)	0 (0)	1 (1.6)	0
Chlorocresol	0 (0)	1 (2.7)	1 (1.6)	0
Chloroquinadol	1 (3.7)	0 (0)	1 (1.6)	0
Colophonium	0 (0)	1 (2.7)	1 (1.6)	0
Copper sulfate	0 (0)	1 (2.7)	1 (1.6)	0
Epoxy resin	1 (3.7)	0 (0)	1 (1.6)	0
Gold sodium thiosulfate	0 (0)	1 (2.7)	1 (1.6)	0
Propyl-4-hydroxybenzoate	1 (3.7)	0 (0)	1 (1.6)	0
Sorbitan monooleate	0 (0)	1 (2.7)	1 (1.6)	0
Mean number of reactions	1.07	1.66	1.42	—
≥1 Positive reaction	13 (48.1)	21 (56.8)	34 (53.1)	—

MCI/MI, methylchloroisothiazolinone/methylisothiazolinone.

frequent relevant allergens were fragrance mix I (n = 6), *M. pereirae* (n = 5), cocamidopropyl betaine (n = 2), and benzocaine (n = 2). Six patients (9%) tested positive to their own products including topical anesthetics (benzocaine and cinchocaine), topical antifungals, and pimecrolimus cream.

Positive and relevant results are shown in Table 1. There were no significant differences in allergen positivity rates between men and women, even when fragrance, medicament, and preservative reactions were combined. After patch testing, the most common diagnosis was atopic dermatitis, followed by ACD, irritant dermatitis, psoriasis, and lichen sclerosus. The mean number of reactions in patients with a final diagnosis of ACD was 3.3 compared with 0.8 for patients with a primary diagnosis other than ACD. For patients with a final diagnosis other than ACD, the common reactions were similar to the total population (metals and fragrances).

DISCUSSION AND CONCLUSIONS

We found 30% of patients presenting with anogenital involvement had at least one relevant positive allergen and comparative rates from the literature vary widely, 17% in Belgium¹ to 73% in Scotland.¹² Previous Australian literature describing patch testing in patients with anogenital dermatoses show similar results to ours with top allergens consistently including metals, fragrances, and medicaments, particularly topical anesthetics.^{13–15} A description of selected anogenital allergens and example sources is listed in Table 2.

Fragrances, including *M. pereirae*, may be added to personal care products designed for use in the genital region and are commonly reported allergens in anogenital ACD.^{3,16,17} A study from the Netherlands found that spices and flavors including nutmeg,

TABLE 2. Example Allergens in Anogenital ACD^{3,5,12–22}

Allergen	Description	Potential sources
<i>Fragrances</i>		
Fragrance mix	Mix of fragrances (cinnamyl alcohol, cinnamal, hydroxycitronellal, amyl cinnamal, geraniol, eugenol, isoeugenol, oakmoss absolute)	Personal care products such as washes, shampoos, moisturizers, feminine hygiene products
Fragrance mix II	Mix of fragrances (hexyl cinnamic aldehyde, hydroxyisohexyl 3-cyclohexene carboxaldehyde, farnesol, coumarin, citral, citronellol)	Personal care products such as washes, shampoos, moisturizers, feminine hygiene products
<i>Myroxylon pereirae</i> (Balsam of Peru)	Fragrance sourced from <i>Myroxylon</i> balsamum tree, used as perfume, flavoring and in medicinal products due to mild antiseptic properties	Personal care products such as washes, shampoos, moisturizers, feminine hygiene products
<i>Medicaments and steroids</i>		
Benzocaine	Anesthetic	Topical hemorrhoid preparations, Vagisil (Combe Incorporated)
Tixocortol-pivalate	Marker for group A corticosteroid allergy	Topical steroids including hydrocortisone, methylprednisolone
Budesonide	Marker for group B corticosteroid allergy (cross-reacts with class D2)	Topical steroids including triamcinolone acetonide, halcinonide, desonide, hydrocortisone butyrate
Neomycin	Antibacterial	Over-the-counter antibacterial creams and ointments
<i>Preservatives and antioxidants</i>		
Methylisothiazolinone	Preservative	Cleansers and shampoo, previous relevance in moist-flushable wipes, however banned in leave-on products in Australia 2017
Formaldehyde, quaternium-15, imadizolidinyl urea, diazolidinyl urea, DMDM hydantoin	Formaldehyde and formaldehyde-releasing preservatives	Multiple sources including fabrics, cosmetics, toilet paper
Methyldibromo glutaronitrile	Preservative	Cosmetics and toiletries such as moisturizers, moist flushable wipes, washes, sanitary pads (banned by European Union 2007)
Sodium metabisulfite	Sulfite preservative and antioxidant used in cosmetic, food, and pharmaceutical industries	Topical steroids, anesthetics and antifungals, e.g., Nizoral cream (Janssen-Claig, Berchem, Belgium), cleansers, shampoos, moisturizers
Benzalkonium chloride	Antiseptic	Cosmetics, laundry rinses, bath oils
<i>Others</i>		
Nickel sulfate	Metal	Genital transfer by hands after contact with jewelry, coins, keys, clothing items, cell phones, role of dietary intake in anogenital dermatoses debated
Cocamidopropyl betaine	Surfactant (foaming agent)	Cleansers and shampoo
Wool alcohol (lanolin)	Emulsifier obtained from wool of sheep	Moisturizers and cosmetics

coriander powder, onion powder, and curry powder were the most relevant allergens in patients with vulval dermatoses and avoidance of these spices in food led to significant improvement.²³ This is a unique and interesting finding. The authors suggest that fragrance mix and *M. pereirae* may be markers for spice allergy and that spice contact with the anogenital region occurs via excretion in urine and feces. The authors have also reported a case of vulval dermatitis due to peppermint oil in herbal tea.²⁴

Caine anesthetics are another commonly reported cause of ACD in the anogenital region,^{18–20} likely because of presence in topical hemorrhoid preparations. Benzocaine is also an ingredient in Vagisil (Combe Incorporated, NY), an over-the-counter cream marketed for vaginal irritation. Vagisil was a common allergen in an Adelaide study of vulval pruritus.¹⁴ In addition to the baseline series, it is recommended that testing includes a topical medicament and anesthetic series as well as the patient's own products.²⁵

The corticosteroid series was added for more than half of patients; however, no cases of anogenital ACD due to corticosteroids

were seen. Furthermore, Brenan et al¹³ patch tested 50 patients with vulval dermatoses in Victoria with the corticosteroid series, and despite widespread corticosteroid use in their patients, there was only one positive reaction to budesonide, which was not considered relevant. We saw 3 cases of sensitization to antifungal preparations and 2 of these were relevant. Contact reactions to imidazole antifungals are often irritant; however, ACD may occur to components of the vehicle or the active ingredient (usually miconazole).^{21,22} Allergy to topical estrogens is reported but not common. In a study from the Mayo clinic, there was one reaction to conjugate estrogen of 74 women tested for vulval dermatoses.¹⁶ For use on anogenital skin, medicaments in an ointment base are generally preferred to creams as they contain less preservatives and have increased potency due to occlusion and increased absorption.²⁶

Preservatives are common ingredients in personal care products and topical medicaments and in keeping with the literature were implicated in anogenital ACD in our series. We saw relevant reactions to formaldehyde and formaldehyde-releasing preservatives

(quaternium-15, imidazolidinyl urea, diazolidinyl urea) and other preservatives including methylidibromo glutaronitrile and sodium metabisulfite. We saw one case of anogenital ACD caused by methylchloroisothiazolinone/methylisothiazolinone in moist flushable wipes, and this has been reported elsewhere.⁵ After an epidemic of methylisothiazolinone allergy in Australia, recent data suggest that rates may be decreasing after legislative change in 2017 banning its use in leave-on cosmetic products.²⁷

We found that 16% of patients had a positive patch test reaction to nickel; however, none of these reactions were considered relevant. Lucke et al¹² reviewed women with vulvar dermatoses and argued that nickel may be an important allergen after finding 8 women with positive nickel patch tests who improved after nickel avoidance. The relevance of nickel sensitivity in these cases is debated as the majority have no direct nickel contact with the anogenital region other than the potential for trace metals in recycled paper used to make toilet paper.¹³ Alternatively, nickel transfer from the hands may be the allergen source. Systemic contact dermatitis is another proposed mechanism and a prospective study from Denmark found that 3 of 3 patients with anogenital dermatitis and 21 (68%) of 31 with vesicular hand eczema experienced long-term improvement after adoption of a low-nickel diet; however, there was no control group in this study and numbers are low.²⁸

The limitations of this study include the retrospective design, which introduces inherent issues with data completeness and collection. Patch testing data is relevant to the population tested and results may not be generalizable. Patients may have had concurrent diagnoses, such as lichen sclerosus, in addition to contact allergy; however, the database captured only the top diagnosis for each case. Therefore, we cannot comment on the prevalence of ACD in individual diagnostic groups.

In conclusion, the top positive and relevant allergens seen in our patients with anogenital disease were in concordance with other reports from Australia and the rest of the world. In particular, fragrances are consistently implicated and this reinforces the recommendation that products used on anogenital skin should be fragrance free. Medicaments are common allergens, particularly topical anesthetics, and testing patient's own products is imperative. We found no relevance of nickel reactions; however, a small body of research suggests, in patients with anogenital disease and a positive patch test to nickel without another identified cause, nickel avoidance including trial of low-nickel diet may be beneficial. Allergic contact dermatitis of the anogenital region should be considered in patients with chronic disease, if there is a history of multiple topical contacts or in cases recalcitrant to treatment.

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