

Allergic Contact Dermatitis of the Vulva

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Allergic contact dermatitis is an important diagnostic consideration in the evaluation of patients presenting with vulvar complaints. The high prevalence of contact sensitization in the vulvar region is likely multifactorial. We review the extant literature regarding key predisposing factors in the pathogenesis of vulvar allergic contact dermatitis, as well as the most commonly implicated allergens as identified by a number of retrospective studies and case series. On the basis of our findings, we provide diagnostic and therapeutic recommendations for practicing clinicians.

Contact dermatitis is an important diagnostic consideration in the evaluation of patients with vulvar symptoms. It is a common diagnosis in this population, with estimates suggesting an underlying irritant or allergic contact dermatitis (ACD) may be present in up to 54% of patients presenting to vulvar clinics.¹ Unfortunately, it is also a commonly delayed diagnosis due to both hesitation on the part of patients to report symptoms to providers as well as misdiagnosis by providers due to poor awareness of the spectrum of vulvar disease. Studies have shown that vulvar dermatoses in particular have a tremendous impact on quality of life—a fact that further underscores the importance of early and accurate diagnosis of these conditions.²

Epidemiology

Studies suggest there is a high prevalence of contact sensitization in the vulvar area. Overall, patients with anogenital dermatitis exhibit higher rates of positive patch test results (39%–78%) as compared with a general female adult (35%–40%). Importantly, reported incidences of clinically relevant patch test results for patients presenting with vulvar complaints are likewise high, ranging from 16% to 54%.^{3–9}

Clinical Presentation

Allergic contact dermatitis is a delayed (type IV) hypersensitivity reaction, typically presenting 2 to 7 days after exposure to the inciting antigen. Exposure to a strong allergen results in the development of acute ACD, clinically manifesting as marked edema, erythema, vesicles, and sometimes bullae or ulcerations in the affected area

(Fig. 1). This can rarely lead to generalized reactions, whereby sites of previous contact with the allergen exhibit a similar dermatitis (recall phenomenon). In addition to a severe rash, patients often report severe pruritus or pain, prompting them to rapidly seek care. In contrast to this florid presentation, exposure to weak allergens on either a prolonged or intermittent basis results in the development of chronic ACD, which typically presents with pruritus in conjunction with erythematous to hyperpigmented, variably lichenified, and excoriated plaques. This more subtle presentation can be difficult to diagnose, especially in patients with heavily pigmented skin, where hyperpigmentation may be the only discernible clinical feature.¹⁰

Vulvar contact dermatitis may result from allergen exposure via several routes, including local exposure via direct application of topical products, inadvertent transfer from other body sites, the presence of allergen in secretions in the urine or feces after oral consumption, or systematized contact reactions.¹¹ In 1 study, a higher rate of sensitization was noted among patients with vulvar dermatitis who also had a concomitant perianal dermatitis, suggesting that performing patch testing may be especially relevant in patients with concomitant perianal involvement.¹²

An important consideration in the diagnosis of vulvar ACD is the possibility of vulvar irritant contact dermatitis (ICD), which is more common than its allergic counterpart.^{11,13} Irritant contact dermatitis results from exposure to agents that cause direct (nonimmunologic) injury to keratinocytes and the lipid barrier. Similar to ACD, more robust clinical manifestations, including edema, bullae, and ulceration, are noted after exposure to more severe irritants, whereas more subtle presentations are seen with mild irritants, which can manifest with a mild dermatitis or, in some cases, even stinging and burning in the absence of discernible cutaneous change. Ruling out a concomitant ICD can be difficult, not only because of significant clinical and histological overlap of these conditions but also because many implicated products can exert both irritant and sensitizing effects. For example, personal wipes and vaginal douches contain both various irritant and sensitizing agents.¹¹

In addition to ICD, the differential diagnosis of acute and chronic ACD includes a number of other dermatitides (Table 1).

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Figure 1. Variable presentations of vulvar contact dermatitis: (A) ACD to neosporin presenting with mild erythema and edema; (B) severe irritant erosive ACD to witch hazel; (C) edema, erythema, lichenification, and focal erosions in ACD to benzocaine. Photo credit to Dr Lynette Margesson.

Etiological Factors

A variety of etiological factors underlie the high incidence of ACD in patients with vulvar symptoms. These include features intrinsic to the vulva that are thought to result in a predilection for the development of ACD and ICD, as well as patient-related factors, including, for example, a preexisting vulvar dermatosis or the presence of specific behavioral practices, such as shaving, grooming, and douching. These factors are reviewed in more detail below.

Vulvar Anatomy

The female external genitalia consists of the clitoris, the mons pubis, the labia majora, labia minora, and glandular structures, with marked variation in the physiological characteristics of these anatomic sites.¹⁴ The skin of the labia, mons pubis, prepuce, and perineum is of ectodermal origin and has a keratinized, stratified squamous epithelium. The thickness and degree of keratinization of these structures decrease from the lateral to medial surface of the

labia and from the mons pubis to the anterior portion of the clitoris. Hart's line separates the keratinized epithelium of the labia from the nonkeratinized transitional epithelium of the mucosal vulvar vestibule, which is derived from embryonic endoderm.¹⁵ Based on

TABLE 1. Differential Diagnosis of ACD

Acute presentation: marked vulvar erythema with erosions or bullae	Candida vulvovaginitis Herpes simplex or zoster virus infection Impetigo (<i>Staphylococcus</i> / <i>Streptococcus</i>) Cytomegalovirus Epstein-Barr virus Mycoplasma Tuberculosis Primary syphilis, chancroid Bullous pemphigoid Pemphigus vulgaris Mucous membrane (cicatricial) pemphigoid Linear immunoglobulin A bullous dermatosis Epidermolysis bullosa acquisita Hailey-Hailey disease Epidermolysis bullosa Lichen sclerosis Genital aphthae Behçet disease Crohn disease Acrodermatitis enteropathica Necrolytic migratory erythema Zoon plasma cell vulvitis Severe irritant dermatitis Erythema multiforme, Stevens-Johnson syndrome Bullous fixed drug eruption Erosive/bullous lichen planus Langerhans cell histiocytosis Extramammary Paget disease Squamous cell carcinoma Tinea cruris
Subacute to chronic presentation: scaly, variably lichenified, erythematous plaques	Candida vulvovaginitis Erythrasma Enterobiasis (pinworms) (especially if perianal) Seborrheic dermatitis Inverse psoriasis Atopic dermatitis Lichen simplex chronicus Mild irritant dermatitis Lichen sclerosis Plasma cell (Zoon) vulvitis Vulvar intraepithelial neoplasia Squamous cell carcinoma Basal cell carcinoma Extramammary Paget disease

studies on buccal and vaginal mucosa, the nonkeratinized vulvar vestibule is likely more permeable than the keratinized portions of the vulva and thus more susceptible to exogenous topical agents.^{16,17}

The vulva is exposed to various physiologic irritants, including urine, vaginal secretions, and menstrual blood, sweat, as well as prolonged occlusion, because vulvar skin is often covered by underwear or sanitary pads or occluded because of skin-to-skin contact. As a result of scrubbing, sexual activity, and contact with clothing, it is also exposed to a significant amount of mechanical friction. Studies suggest that the susceptibility of vulvar skin to the development of ICD may be irritant specific.^{18–20}

Immunologic Milieu

The vulva is an immunocompetent tissue with abundant quantities of Langerhans cells capable of inducing a hypersensitivity reaction upon antigen exposure.¹³ In fact, vulvar skin contains a higher concentration of antigen-presenting cells compared with skin at other body sites.²¹ Histological studies suggest that there are some important regional differences in the vaginal epithelial immunologic milieu. Studies in monkeys have revealed a gradient in Langerhans cells density along the genital tract, with the lowest densities in the vaginal fornix and highest in the introitus.²² Distinct regional differences have also been noted in human studies, where the vulva has been noted to contain a markedly higher density of Langerhans cells compared with the vagina (median value of 18.7 as compared with 5.5 per 100 basal squamous cells), and the cervical transformation zone was noted to have the highest proportion of lymphocytes.²³

In a histological study of vulvar skin across the life span, the highest density of immunologic cells was noted within the reproductive years, from 30 years to approximately 55 years.²⁴ Studies in both monkeys and humans further suggest that cyclical variations in menstrual cycle hormones may also impact both genital T-cell function and immunoglobulin levels.^{25,26}

Age- and Hormone-Related Changes

Both chronologic aging and varying ovarian hormone levels, particularly in the setting of puberty, menses, pregnancy, and menopause, are associated with a number of changes in vulvar morphology and physiology. The vulvar epithelium is thickest during a woman's reproductive years, at which time estrogen-mediated cyclical changes in the amount of vulvar parakeratosis are noted with the menstrual cycle. Relative estrogen deficiency during premenarche, postpartum and lactation periods, menopause, and oral contraceptive use may underlie impaired barrier function of the vulvar epithelium.^{11,27}

During pregnancy, the vulvar, vaginal, and perineal connective tissue relaxes, and local increases in blood volume and venous distensibility affect coloration and occasionally result in vulvar varicosities.²⁸ With menopause, the pH of the stratum corneum rises, resulting in barrier defects due to deficient intercellular lipid content and cell cohesion, slower barrier recovery after injury, and increased susceptibility to microbial colonization and infection.^{21,29}

Menopause is also associated with loss of subcutaneous fat in the labia and vestibule, as well as vaginal mucosal atrophy.

Interestingly, studies comparing irritant responses in premenopausal and postmenopausal women have failed to identify significant age-related changes in vulvar susceptibility to irritants, although differences in other cutaneous sites have been noted (with postmenopausal women being less susceptible to irritants at extramucosal sites).¹⁸ It has been speculated that the postmenopausal vulva may also be less susceptible to the development of ACD because of the declining local immune response, although this has not been formally evaluated in comparative studies.^{21,30} Nevertheless, vulvar, perineal, and perianal dermatitis are a significant issue among this cohort of patients, likely due to increased incidence of incontinence, with resulting prolonged exposure to urine and fecal enzymes, which elevate the vulvar pH, altering barrier function and increasing susceptibility to microbial colonization and friction damage.^{28,31–33}

A small but growing literature is exploring the potential role of derangements in the microbiome in the pathogenesis of vulvar and vaginal disease. For example, 1 study found that women postmenopause with signs of vulvovaginal atrophy on examination had 25-fold greater odds of exhibiting a vaginal microbiota profile characterized by a low abundance of *Lactobacillus* species.³⁴ Some evidence also suggests menstruation may induce cyclical alterations in the microbiome of the labia minora.³⁵ Interestingly, several studies suggest estrogen-deficient states are associated with a unique *Lactobacillus*-deficient microbiome profile and conversely that hormonal replacement therapy seems to alter the microbiome by increasing the abundance of *Lactobacillus* species.^{36–38} This may be at least in part mediated by the role of estrogen in supporting glycogen deposition in the vaginal epithelium, which is subsequently metabolized by local bacterial communities to produce lactate and other organic acids. Further research is needed to clarify the relationship between estrogen, the vulvar and vaginal microbiome, and a variety of diseases of the lower female genital tract.

Preexisting Dermatoses

Vulvar ACD can occur both as a primary process and as a secondary complication in patients with a preexisting vulvar dermatosis. The latter should be suspected in patients with sudden exacerbations in previously well-controlled or resolved vulvar disease or a blunted response to an otherwise efficacious treatment. Importantly, several studies suggest that this subgroup may be particularly susceptible to the development of ACD, accounting for the majority of patients with positive patch test results. For example, in 1 retrospective study of 135 patients patch tested for persistent vulvar symptoms over a 5-year period, only 4% of the patients found to have ACD via patch testing did not have a preexisting vulvar dermatosis.⁶ Among this subgroup, the most common underlying diagnoses among those with clinically relevant positive patch test results were atopic dermatitis (36%) and lichen sclerosis (23%). Other less common concomitant dermatoses included human

papillomavirus, LP, lichen simplex, psoriasis, seborrheic dermatitis, vulvodynia, and candidiasis.⁶ Similarly, in a retrospective chart review completed by our group of 26 patients who underwent patch testing for vulvar complaints, 56% of the patients had a concomitant vulvar dermatosis, most commonly lichen sclerosis.⁹ Other preexisting vulvar diagnoses among this cohort included lichen simplex chronicus, atopic dermatitis, condyloma acuminatum, psoriasis, and Paget disease.⁹ At present, the existing evidence does not decisively point to an increased risk of ACD among patients with any particular preexisting vulvar dermatosis.³⁹

In a similar vein, one might hypothesize that the chronicity of vulvar symptoms may be an important risk factor for the development of ACD due to progressive impairment in barrier function as well as increased exposure to various over-the-counter and physician-prescribed therapies. However, conflicting findings have been reported in the literature, and additional studies are needed to further elucidate the relationship between chronicity of vulvar disease and risk of ACD.^{8,9,39}

Atopic Diathesis

Although theoretically plausible, the importance of an atopic diathesis to the subsequent development of vulvar dermatitis remains unclear. In 1 study of patients with vulvar dermatitis, 97% had a history of atopy or concomitant seborrheic dermatitis, suggesting that atopic diathesis may correlate with a predisposition to develop vulvar ACD.⁴ Contrasting these findings, another study found a lower rate of ACD among atopic patients with vulvar symptoms, with a rate of clinically relevant positive patch test results of 42% among atopic patients compared with 50% in nonatopic patients.⁸

Other Patient-Related Factors

Other important factors that may be relevant to the pathogenesis of vulvar ACD in patients include obesity and limited mobility, both of which can worsen occlusion, increase shear forces, and result in an inability to inspect and clean the vulva. Poor nutritional status may lead to skin breakdown and/or impaired or prolonged wound healing and thus a compromised skin barrier. Concomitant local infections, for example, genitourinary infections resulting in urinary incontinence or gastrointestinal infections, resulting in diarrhea, can result in the development of ICD, which may predispose to or further exacerbate ACD.

Exogenous Factors: Allergens and Irritants

A variety of agents have been implicated in the development of ACD of the vulva and, more broadly, anogenital regions. We review the extant literature regarding the most commonly implicated allergens, which draws in large part from retrospective and a few prospective studies in patients with chronic vulvar complaints. We also briefly review the most common culprits of vulvar ICD because this is a frequent concomitant diagnosis.

Fragrances

Fragrances are an important cause of ACD and vulvar ACD. Most standard patch test series include fragrance mix I, *Myroxylon pereirae* (balsam of Peru), and fragrance mix II. Fragrance mix I is composed of amyl cinnamal, cinnamyl alcohol, cinnamal, eugenol, geraniol, hydroxycitronellal, isoeugenol, oak moss absolute, and sorbitan sesquioleate. Fragrance mix II is composed of lylal, citral, citronellol, farnesol, hexyl cinnamic aldehyde, and coumarin. Balsam of Peru is a naturally occurring compound derived from the South American fir tree, *M. pereirae*. It includes benzyl acetate, benzyl alcohol, cinnamic acid, cinnamic alcohol, cinnamic aldehyde, eugenol, and isoeugenol.

Sensitivity to fragrance mixes I and II, as well as *M. pereirae*, has been reported in numerous studies.^{4-6,12,40-44} In a retrospective chart review of patch test results for 25 patients with refractory vulvar pruritus or burning conducted by our group, fragrances represented the most frequent allergen group, accounting for 18% of all positive results.⁹ Keeping with these findings, Warshaw et al⁴⁵ conducted a retrospective, cross-sectional analysis of the North American Contact Dermatitis Group database, including 347 patients (both male and female) with anogenital disease from 1994 to 2004, finding that fragrances were among the most frequent allergens, including *M. pereirae*, fragrance mix I, and cinnamal, each noted to be positive in 26.7%, 20.6%, and 5.5% of patients with anogenital dermatitis, respectively. Among a cohort of 21 patch-tested patients who presented to the dermatogynecology clinic at Mercy Hospital (Melbourne, Australia), 12% of clinically relevant positive reactions were attributed to fragrances.⁴¹ Among a cohort of 201 patients with vulvar and/or perianal dermatitis, fragrances accounted for the largest proportion of positive reactions, occurring in 7% of the patients.¹² In other studies, fragrance sensitization was less frequently detected but almost always clinically relevant.⁴⁶ Overall, given the breadth of products and medicaments containing fragrance that are marketed for the treatment of vulvar complaints, fragrance allergy is an important consideration in the evaluation of these patients.

Preservatives

In the aforementioned study by Warshaw et al,⁴⁵ a high rate of clinically relevant reactions to preservatives was reported, including sensitization to quarternium-15 (13.7% of patients with anogenital dermatitis), paraben mix 12% (8.2%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (6.9%), ethylenediamine dihydrochloride (5.7%), and 2-bromo-2-nitropropane-1,3-diol (5.5%). Sensitivity to ethylenediamine hydrochloride, a stabilizer present in various topical preparations, has also been reported in various studies. In a cohort of 50 patients seen in a dermatogynecology clinic who were patch tested for suspected contact allergy, reactions to ethylenediamine represented 8% of clinically relevant patch test results.⁴¹ It is present in the early formulation of Mycolog, a widely used antifungal cream. Although subsequent formulations no longer contain this allergen, it continues to be an important stabilizer in topical products, particularly generic preparations of triamcinolone acetonide, nystatin, and gentamicin creams.

More recently, numerous case reports have implicated the preservatives methylchloroisothiazolinone MCI/MI in cases of vulvar, perianal, and perineal ACD in both children and adults in the United States.^{47–54} Methylchloroisothiazolinone/methylisothiazolinone is used in many industrial (paints, household cleaning products, metal working fluid) and cosmetic (shampoos, skin care products, sunscreens) products and was previously a well-known allergen in Europe, where its use has since been restricted because of the high rates of sensitization. Because of its demonstrated antimicrobial effects in broad pH ranges and at low concentrations, it has become an increasingly popular ingredient in moist toilet paper products and other cosmetics, and consequently increasing rates of sensitization to MI and MCI/MI have been noted, so much so that the American Contact Dermatitis Society designated MI as allergen of the year in 2013.⁵⁵ Methylchloroisothiazolinone is also found in VersaBase topical preparations (gel, lotion, cream, foam), which may be used as a base in compounded topical medicaments for the vulvovaginal area.

In the study of Marren et al,⁶ reactions to preservatives represented only a minority of clinically relevant positive patch test results (5 of 78 reactions). The implicated agents included stearyl alcohol (a rare allergen), imidazolidinyl urea, chloroacetamide, and propylene glycol. Reactions to other preservatives including methyldibromo glutaronitrile (MDBGN) 0.3%, 2-phenoxyethanol 1%, sodium metabisulfite 5% aqua, and thimerosal 0.1% have also been reported.³

Medicaments

A variety of topical treatments are used in the management of vulvar pruritus, including corticosteroid creams/ointments, anti-itch creams (eg, Vagisil), cleansers, antibiotics, antifungal/antiyeast creams, and hormonal creams. Many of these have been implicated in vulvar ACD. In fact, in several studies, medicaments or their constituents were the most commonly identified allergens in women with vulvar pruritus.^{6,43,45,46,56} In 1 study, among the minority of patients with positive patch test results without a preexisting vulvar dermatosis for which they received medical treatment, all demonstrated reactivity to multiple medicaments, suggesting that both provider- and patient-initiated therapies are important triggers in the development of vulvar ACD.⁶

For example, in a retrospective chart review of 135 patients for whom patch testing was performed in the workup of persistent vulvar symptoms, 37 of the 39 patients with clinically relevant positive patch test results were sensitive to at least 1 medication. Within this subgroup, the most common offender was framycetin (an aminoglycoside antibiotic); this was attributed to cross-reactivity with neomycin in the majority of the cases, although 1 patient did report a history of direct contact with framycetin sulfate in Framycort.⁶ These results are replicated in several other studies, suggesting neomycin is likely the most common allergen in topical antibiotic medicaments.^{6,56} For example, in a study by Al-Niaimi et al⁴⁶ of 282 patients in a large teaching hospital over a 6-year period, topical antibiotics (specifically neomycin and framycetin) were, along with

anesthetics, the most common cause of sensitization among the 49% of clinically relevant patch test results. In the retrospective analysis by Warshaw and colleagues,⁴⁵ 9.7% of patients with anogenital ACD had clinically relevant reactions to neomycin, whereas 5.5% reacted to bacitracin. Streptomycin sulfate (which also cross reacts with neomycin) was a clinically relevant allergen in a series of 50 patients with vulvar pruritus who underwent patch testing.⁷ In addition to streptomycin sulfate and framycetin sulfate, other antibiotics that cross-react with neomycin include bacitracin, kanamycin, gentamicin, and tobramycin.⁵⁷

Topical antifungals have also been implicated in vulvar ACD. In 1 retrospective review of 90 patients who underwent patch testing for suspected vulvar ACD, terconazole emerged as the most common allergen for which clinical relevance could be established.⁴² In a retrospective chart review of 201 patients with suspected vulvar or perianal dermatitis, antifungal allergies were noted in 3% of the patients with vulvar dermatitis and 4% of the patients with both vulvar and perianal involvement.¹² A large retrospective review of 1008 patients with anogenital complaints registered in the Information Network of Department of Dermatology from 1992 to 1997 reported that 1.8% of patients with positive patch test results exhibited sensitization to clotrimazole.⁵⁸ Rare cases of sensitization to nystatin have also been reported.⁵⁹

Positive patch tests to clobetasol and tixocortol pivalate have been noted in patients who have been prescribed topical steroids for preexisting dermatoses, including lichen sclerosis and vulvar eczema.⁶ Corazza et al³⁹ reported a rate of topical steroid sensitization of 4.5% in a cohort of 66 patients with vulvar pruritus. In the aforementioned study of 282 patients by Al-Niaimi et al,⁴⁶ steroid allergies corresponded with only 2% of positive patch test results. Allergic reactions to both the steroid molecule and its vehicle components were reported; for example, a reaction to sodium metabisulfite, which is found in Trimovate (GlaxoSmithKline, London, United Kingdom), was identified in 1 patient.⁴⁶ Finally, in a large retrospective study by Warshaw et al,⁴⁴ corticosteroids emerged as one of the most common relevant allergens; reactions to hydrocortisone-17-butyrate (13.5%), clobetasol-17-propionate (10.8%), budesonide 0.1% (9.7%), and tixocortol-21-pivalate (6.9%) were noted. The high rate of clinically relevant positive reactions to topical steroids among this subgroup may be due to increased penetration and/or chronic use. Markedly higher rates of topical steroid penetration in vulvar and scrotal skin as compared with the forearm have been demonstrated in several studies.^{20,60}

Topical anesthetics are a frequent cause of vulvar ACD. The ester anesthetics, for example, benzocaine, procaine, and tetracaine, seem to be of particular importance, although sensitization to the amide anesthetics (bupivacaine, lidocaine, dibucaine, mepivacaine, prilocaine) has also been reported.⁶¹ Reactions to caine mix, cinchocaine, were among the most common cause of sensitization in the cohort of patients studied by Al-Niaimi et al.⁴⁶ Ester anesthetics were noted to be a major contributor to ACD in several other studies.^{41,56} In the study by Warshaw et al,⁴⁵ clinically relevant reactions to anesthetics among patients with anogenital ACD were

high, with 12.5% of the patients reacting to benzocaine and 13.5% to dibucaine. Interestingly, in a retrospective chart review of patch test data collected from 1999 to 2003 for 1168 patients in Germany, Kügler et al⁶² uncovered a significantly higher frequency of sensitization to topical anesthetics (cinchocaine, bupivacaine, benzocaine) among patients with anogenital dermatoses as compared with a general patch test population. This may be due to the widespread presence of ester anesthetics in a variety of over-the-counter antipruritic preparations, such as Vagisil, which contains benzocaine. Importantly, ester anesthetics can cross-react with a variety of substances, including para-aminobenzoic acid, paraphenylenediamine, aniline and azo dyes, sulfa drugs, and thiazide diuretics.⁵⁷

Haverhoek et al⁸ patch tested 21 patients to specific topical medications, including Vagisil, Paraderm Plus, Pevaryl, Ovestin, Resolve, Canesten, Lavender oil in Essence, Nilstat, Hydraderm cream, and tea tree oil. Seven of the 21 patients exhibited reactions to the tested products, including 3 reactions to Vagisil and 5 to tea tree oil, although the clinical relevance of the latter was in question. The authors concluded that the reactions were likely driven by the presence of benzocaine, given its established role as a vulvar allergen; other ingredients in Vagisil include resorcinol, methylhydroxybenzoate, and sodium sulfite anhydrous.

Few case reports implicate antiseptics as relevant vulvar allergens. Adachi et al⁶³ report 1 case of anaphylaxis after vaginal application of povidone-iodone solution as a disinfectant. In a series of 18 patients with genital contact dermatitis to 3% cetrimide and 0.3% chlorhexidine antiseptic solutions, none had a positive patch test, suggesting that these agents were most likely inducing an irritant dermatitis.⁶⁴

Reactions to constituents in female hygiene sprays are most frequently irritant in nature. Fisher⁶⁵ performed patch tests in patients who developed vulvar dermatitis after the application of female hygiene sprays and uncovered only 3 allergic reactions, 2 from benzethonium chloride and 1 from chlorhexidine.

Nickel

Positive patch test results to nickel and cobalt chloride are common in patch test studies of vulvar dermatitis, but the clinical relevance of these findings is a subject of ongoing debate.^{6,8,40,46,66} Lucke et al⁶⁶ reported sensitization to nickel in 31% of 55 patients with vulvar symptoms who were patch tested. Given that approximately half of such patients exhibited resolution or improvement in symptoms with adaption of a nickel-free diet and avoidance of topical contact with nickel, the authors concluded that this was a relevant allergen. In various subsequent studies, sensitization to nickel has been prominent; however, a history of relevant direct vulvar contact with nickel could not be established. For example, in 1 study, reactions to nickel did not correlate with shaving.⁸ Furthermore, investigators have not attempted to replicate the findings of Lucke et al by investigating a response to nickel avoidance among a subset of patients demonstrating positive patch results. It thus remains unclear whether nickel is a relevant vulvar allergen either via direct topical exposure or a “pass-through” mechanism or if this high proportion simply reflects the higher reactivity to nickel in the general population.

Other Allergens

Botanical Extracts

Studies suggest that the use of topical formulations with botanical extracts among patients with chronic vulvar complaints is high and possibly increasing. In 1 recent study, more than 60% of patients with chronic vulvar complaints reported use of botanical products, with the majority citing a belief that such preparations were safer than their synthetic counterparts as the rationale.³⁹ Patients reported use of a variety of formulations, including cleansers, creams, vaginal suppositories, and plugs. A large number of botanicals were used, the most common of which were chamomile, *Aloe vera*, and *Calendula officinalis*. Approximately 16.7% of patients reported adverse reactions to these topical products, of which 42.8% had a clinically relevant positive patch result to a standard series, and 28.7% had a relevant reaction to a botanical integrative series (*Arnica montana*, Compositae mix).³⁹ The authors attribute this low rate of reactivity to the botanical series to various factors, including the limited availability of standardized botanical allergens for commercial testing, as well as the possibility that patients were sensitized to preservatives and fragrances in these botanical products, rather than the plant extract itself. Notably, data from the broader ACD literature seem to suggest that botanical extracts are in themselves important allergens.^{67–71}

Flavors and Spices

In a retrospective chart review of 53 patients who were patch tested for the workup of chronic anogenital complaints in the Netherlands, flavors and spices emerged as an important cause of ACD, accounting for approximately half of relevant allergens in 28% of patients. Specifically, sensitization was noted to peppermint oil, nutmeg powder, coriander powder, curry mix powder, and onion powder. Patients were subsequently advised to avoid these potential allergens and experienced mild to dramatic improvements in their dermatitis in most cases, confirming the clinical relevance of these patch test findings.³ This is presumably due to exposure to the orally administered allergen via excretion in urine or feces. These findings have not been replicated in subsequent studies.

Emollients/Vehicles

Propylene glycol is used as a vehicle, emulsifier, or solvent in various cosmetic formulations and topical medicaments, including many topical steroids. It is a known precipitant of both irritant and ACD. In a retrospective analysis of cross-sectional data of 23,359 patients who underwent patch testing, 3.5% had positive reactions to propylene glycol.⁷² Interestingly, a much higher rate of clinically relevant reactions to propylene glycol (10.3%) was noted in a cohort of 347 patients with anogenital signs of symptoms who were referred for patch testing, although paired comparisons between patients with and without anogenital ACD in this study failed to reveal statistically significant difference in the rates of propylene glycol reactivity between these groups.⁴⁵

Lanolin is a widely used emollient present in Aquaphor, A and D ointment, and various other topical formulations and medicaments. It is analogous to sebum and derived from the sebaceous gland of

sheep.⁷³ In the same study by Warshaw and colleagues,⁴⁵ lanolin alcohol likewise emerged as a common clinically relevant allergen among patients with anogenital ACD, occurring in 6.9% of patients.

Contraceptives

Sensitization to chemicals in rubber, especially mercaptobenzothiazole, via condom exposure or diaphragm use underlies various case reports of vulvar dermatitis.^{74,75} In the study by Washaw et al,⁴⁵ 6.9% of patients with anogenital ACD reacted to carba mix, and 1.4% reacted to thiuram mix, both of which are potential allergens in condoms. Allergic contact dermatitis to natural latex has been reported in mostly males but also in females presenting with vulvovaginitis.^{74–76} Isolated case reports have also implicated nonoxynol-9, a surfactant-effective spermicide, as well as Tectol, a spermicidal lubricant, in cases of genital ACD.^{77,78}

Sanitary Napkins

Williams et al⁷⁹ report 20 cases of ACD to MDBGN, one of which was a patient with vulvar erythema who was found to be sensitized to the MDBGN-containing adhesive in her sanitary pad. Methyltribromo glutaronitrile is a biocide that is a component of the preservative Euxyl K400 and is also present in adhesives. Overall, these cases represented a small percentage (0.7%) of the 2837 patients who were patch tested in their institution from 1993 to 2004. Although there are various other case reports of patients with MDBGN sensitization, this does not seem to be a major vulvar allergen.

Acrylates are monomers that polymerize to form plastics and are ubiquitous in both industrial and personal care products, including the absorbent material within feminine hygiene pads. Giroux and Pratt⁸⁰ report a case of severe vulvar ACD in a patient with known sensitization to methacrylates after use of Poise thin incontinence pads. Cases of both isolated genital and subsequent systemic dermatitis secondary to acrylates in female hygiene pads and incontinence pads have also been reported.^{80,81} Because of the rising popularity of methacrylate-based gel and acrylic nail varnishes, a rising incidence in occupational (and nonoccupational) cases of methacrylate ACD has been noted, typically presenting with a periungual or digital pulp dermatitis. This is a potentially important sensitizing source or source of digital transfer/exposure to the vulvar area.⁸²

There are also a few case reports of recurring vulvar dermatitis secondary to sensitization to colophony (rosin) in sanitary pads. Deodorized pads and tampons have been specifically implicated in cases of vulvar ACD due to sensitization to fragrance.⁸³

Common Culprits of ICD

The differential diagnoses for ACD of the vulva should invariably include ICD because it is more common than ACD and often coexists with ACD. It is important to inquire about potential prolonged exposure to feces, semen, urine, sweat, and abnormal vaginal discharge as potential irritants.¹¹ Excessive bathing and exposure to harsh soaps and detergents, irritants in douches and other feminine hygiene products, lubricants, and spermicides are also common

causes. Perhaps worth mentioning is how daily use of pads and panty liners also contribute to irritation due to friction. As with ACD, various topical medicaments can exert a potent irritant effect, including topical formulations with alcohols, propylene glycol, phenols, bichloroacetic acid, and trichloroacetic acid. Chemodestructive therapy with fluorouracil, imiquimod, podophyllin, and cantharidin are likewise considerations.¹¹

SUMMARY AND IMPLICATIONS FOR MANAGEMENT

A growing literature is increasing our understanding of the pathogenesis and etiologies of vulvar ACD. In our review of the extant literature, fragrances and medicaments were among the most important allergens (Table 2), accounting for a majority of clinically relevant reactions in several studies. Sensitizing fragrances were identified in a large number of sources, including cleansers, douches, and neutralizers in topical medicaments, such as hemorrhoid creams. Sources of medicament-related allergens were broad, including topical steroids, antifungals, antibiotics, and anesthetics. Importantly, these reactions were relevant in both patients with and without a preexisting vulvar dermatosis, suggesting both provider- and patient-initiated therapies may contain culprit allergens. Indeed, many of the allergens listed in Table 2 are present in widely available medicaments and topical formulations. On the basis of these findings, we recommend obtaining an exhaustive history of preceding and current topical medicament exposure, including prescription, over-the-counter, and alternative medicaments, as well as cleansers, personal hygiene products, and contraceptives used both by the patient and intimate partners. Given the high frequency of fragrance allergies in this cohort, we recommend advising patients with any vulvar dermatitis to avoid fragrance-containing products on presentation, given that this may hasten resolution or prevent subsequent development of a fragrance-mediated vulvar ACD.

Preservatives are likewise important allergens, with rates of sensitization reflecting temporal trends in manufacturer use of these agents. In recent years, the preservative MCI/MI has become a prominent culprit not only of ACD in general but also in the pathogenesis of vulvar and anogenital dermatitis, often in the setting of moist toilet paper use and feminine wipes. Other preservative allergens were most often found in cosmetic products and topical medicaments designed for direct use in genital or in extragenital sites, whereby inadvertent manual transfer results in genital contact with the allergen. Various vehicles as well as allergens in personal care products (sanitary napkins, incontinence pads) and contraceptives were also relevant but less frequent culprits of ACD.

The evidence implicating potential pass-through allergens in the pathogenesis of vulvar ACD is quite limited but compelling, given the impressive rates of resolution after adherence to an allergen-restricted diet. In select patients (especially if there is a perianal component), consideration of a nickel-free or spice- and flavoring-restricted diet may be of clinical utility. Likewise, the broader ACD literature suggests that botanical extracts are

TABLE 2. Allergens Implicated in Vulvar and Anogenital ACD in the Literature

Allergen Class	Allergen
Fragrances	<i>M. pereirae</i> (balsam of Peru)
	Fragrance mix I and II
	Cinnamal (or cinnamic aldehyde)
	Eugenol
	Isoeugenol
	Hydroxycitronellal
	Perfume mix
	Hydroxyisohexyl 3-cyclohexene carboldehyde
	Quaternium-15
	Paraben mix
Preservatives	MCI/MI
	Ethylenediamine dihydrochloride
	2-Bromo-2-nitropropane-1,3-diol
	Stearyl alcohol
	Imidazolidinyl urea
	Chloroacetamide
	MDBGN
	2-Phenoxyethanol
	Sodium metabisulfite
	Thimerosal
Medicaments	Kathon
	Diazolidinyl urea
	Formaldehyde
	Bronopol
	<i>Antibiotics:</i>
	Framycetin sulfate
	Neomycin
	Bacitracin
	Streptomycin sulfate
	Polymyxin
	<i>Antifungals:</i>
	Terconazole
	Clotrimazole
	Miconazole
	Nystatin
	<i>Corticosteroids:</i>
	Hydrocortisone-17-butyrate
	Clobetasol-17-propionate
	Budesonide 0.1%
	Tixocortol-21-pivalate
	Anesthetics: esters (benzocaine, tetracaine, procaine), amides (dibucaine, lidocaine, cinchocaine)
	Bufexamac
	Crotamiton
	<i>Antiseptics</i>
	Chlorhexidine
	Povidone-iodone
	Cetrimide
	Benzethonium chloride
	Mercuric chloride
	Gentian violet
	Phenylmercuric salts
	Thimerosal
	Potassium dichromate

TABLE 2. (Continued)

Allergen Class	Allergen
Metals	Nickel sulfate Cobalt/cobalt chloride hexahydrate
Botanical extracts	<i>Arnica montana</i> Compositae mix Jasmine Oak moss Jojoba oil*
Spices and flavorings	Peppermint oil Nutmeg powder Coriander powder Curry mix powder Onion powder
Emollients/vehicles	Propylene glycol Lanolin alcohol Glycerin Jojoba oil*
Miscellaneous	
Contraceptives	Mercaptobenzothiazole Carba mix Thiuram mix Latex Nonoxynol Tectol Hexylresorcinol Oxyquinoline sulfate Quinine hydrochloride Phenylmercuric acetate, butyrate
Sanitary napkins	Acrylates MDBGN Colophony (rosin)
Nail polish	Toluene-sulfonamide formaldehyde resin
Douches	Oil of eucalyptus Thymol
Dyes	<i>p</i> -Phenylenediamine

*Listed under both emollients/vehicles and botanical extracts.

important sources of general ACD, but their role in the pathogenesis of vulvar ACD remains unclear. Further studies are needed to clarify the importance of these nonstandard allergens to the pathogenesis of vulvar ACD.

Several studies in the literature suggest that patients with preexisting vulvar dermatoses may comprise a majority of those with vulvar ACD, although the risk of ACD does not seem to be increased among patients with any particular vulvar disease. Patients with vulvodynia represent an exception to this finding, as patch testing has not proven to be helpful in this particular subgroup.^{11,66} The chronicity of vulvar disease may be another important risk factor for developing vulvar ACD. Several mechanisms could account for these findings, including increased local topical exposures and progressive barrier impairment. Regardless, these findings suggest ACD (and more generally, a multifactorial etiology) should be a prominent diagnostic consideration in patients with chronic or particularly refractory vulvar disease.

On the basis of these findings, we recommend that all patients with suspected vulvar ACD undergo patch testing with a standard series, such as the North American Contact Dermatitis Group standard series or the American Contact Dermatitis Society Core allergen series. The TRUE test alone may miss important allergens, including MI/MCI, as well as various medicaments and fragrances. For example, with regard to medicaments, the TRUE test includes only neomycin sulfate, caine mix, tixocortol-21-pivalate, budesonide, hydrocortisone-17-butyrate, and bacitracin. Although it includes fragrance mix and *M. pereirae*, fragrance mix II is omitted. Given the high number of potential botanical allergens and low utility of patch testing with a botanical series as demonstrated in current studies, we recommend testing with the patient's own products if a botanical allergy is suspected.

Additional diagnostic testing may be particularly helpful in patients with more florid presentations including bulla and erosions, where biopsy for hematoxylin-eosin and direct immunofluorescence may reveal a primary immunobullous disorder. The presence of marked fissuring, crusting, or pustules is suggestive of concomitant infection, which should be evaluated with bacterial cultures, potassium hydroxide microscopy, and fungal culture or viral culture or direct fluorescent antibody, as deemed appropriate by the evaluating clinician. Given various topical antimicrobial medicaments have been implicated in vulvar ACD, it may be prudent to treat local infections with systemic agents, whenever possible.¹¹ Switching from a cream to ointment-based formulation may also prove to be less irritating and more soothing.

Management of confirmed vulvar ACD starts with prompt removal of the allergen. Counseling on vulvar hygiene and gentle skin care is essential. In general, patients should be advised to bathe at most once daily using only lukewarm water to the affected area. Cleansing should be performed with fingertips, rather than washcloths and sponges. In addition, patients should be advised to avoid soaps or use a fragrance-free, pH-neutral soap or nonsoap cleanser. This should be followed by gentle drying of the area using a tapping motion (rather than rubbing) and liberal application of gentle, nonallergenic emollients (preferentially plain petrolatum or other bland emollient). Practices that may contribute to occlusion and friction, such as wearing synthetic underwear, tight clothing, and pantyhose, should be avoided. We recommend loose-fitting cotton underwear and stockings (thigh-high/knee-high or the crotch cut-out) until the dermatitis has resolved.

Contributors to impaired barrier function should be addressed. In the appropriate clinical context (postmenopausal or other known estrogen-deficient state) and in the absence of contraindications, topical estrogen therapy can be considered with caution, because many of these topical formulations can in themselves contain various allergens. For example, both Premarin and Estrace include propylene glycol. Estrace additionally includes stearyl alcohol, which is a rare allergen. When appropriate, patients should be referred to urogynecology for evaluation and management of urinary incontinence.

Corticosteroids are the cornerstone of treatment. Depending on the degree of clinical inflammation and symptoms, we recommend

starting a trial of low-potency to midpotency topical steroid ointment until the dermatitis has resolved. Twice-daily dosing for a period of 2 to 4 weeks will lead to resolution in most cases. It is important to keep in mind that in select cases topical corticosteroids (by virtue of the steroid molecule itself or preservatives and vehicles in the topical formulation) can actually precipitate vulvar ACD. If there is suspicion for this, we recommend patch testing to a corticosteroid panel and switching to desoximetasone, which is less frequently implicated in ACD. Given the presence of formaldehyde-releasing preservatives in various cream formulations, we additionally recommend use of ointment (rather than cream) formulations whenever possible. Ointment also allows better penetration and may cause less stinging and burning.

Treatment with systemic (oral or intramuscular) steroids may be indicated for severe, persistent, or topical steroid-refractory cases. Courses of oral prednisone 0.5 to 1.0 mg/kg for 1 to several weeks may be required, depending on severity of dermatitis and symptoms.

For patients with severe pruritus, we recommend addition of sedating oral antihistamines, such as hydroxyzine. Topical antihistamines (topical Benadryl) should be avoided because it is a known contact sensitizer.

The findings of our review must be interpreted in light of the limitations of the existing literature. Most studies are retrospective in nature and thus subject to memory bias in patient recollection of topical products that were used. In addition, because of both small sample sizes in the majority of studies and the high number of allergens implicated in ACD, small numbers of clinically relevant reactions to particular allergens were identified, precluding interpretation of broader trends or clinical features that might be associated with each allergen. Finally, variability between studies in thresholds for determining clinical relevance can limit broader conclusions about the importance of various allergens to vulvar ACD.

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