ALLERGIC CONTACT CHEILITIS

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Allergic Contact Dermatitis (ACD) is an important disease, which notably affects 14.5 million Americans each year.[1] The economic impact of this disease is high in terms of both patient morbidity and loss of income, school and work, not to mention significant expenditures for visits to health care providers and for medicaments.[1] Once patch testing is performed and a culprit has been identified, education becomes the critical intervention to ensure adherence to an avoidance regimen. With allergen avoidance, remission of the dermatitis ensues. If patients are unable to comply with the avoidance regimen, they become at risk for recurrent or sustained dermatitis or progression to a systematized presentation.[2,3] In fact, education of the patient often begins before the diagnostic patch test is ever placed. This ensures that the patient has an appropriate understanding of potential outcomes, including his or her central role in both the disease and treatment.

During the initial consultation, patients are often taught about the pathophysiology of ACD: its delayed presentation; its relationship with the immune system (sensitization to a chemical and then elicitation of a dermatitis with re-exposure); and its occurrence at any point in time, even to something that the patient has been using regularly for a short period of time or even intermittently for years. In certain cases, the topics of the other key players, such as irritant contact dermatitis (ICD) and contact urticaria, may be explained, as history (not patch testing) can point to these as the correct diagnosis for the patient. It is important to note that ICD, the most prevalent form of contact dermatitis, can at times precede, or be a concomitant diagnosis, with ACD.[4,5] Unlike ACD, ICD is not immune-mediated, but occurs secondary to contact with an irritating or abrasive substance. Contact urticaria (wheal and flare reaction), on the other hand, represents the least prevalent form of contact dermatitis. It is important to note that it is an immune-mediated phenomenon whose hallmark is an IgE and mast cell-mediated immediate-type hypersensitivity reaction. We acknowledge this form of hypersensitivity due to the severity of the potential deleterious anaphylactic type reactions and direct the reader to key sources.[6,7,8]

In this section focus, we highlight ACD and explore top relevant allergens, regional-based dermatitis presentations, topic-based dermatitis presentations and clinical tips and pearls for diagnosis and treatment.

ALLERGIC CONTACT CHEILITIS

Contact cheilitis is a term used to describe inflammation of the lips, most often caused by either irritant contact cheilitis (ICC) or allergic contact cheilitis (ACC).[9] This inflammation can cause a variety of signs and symptoms, such as dryness, scaling, crusting, fissuring, erythema, edema and/or angular cheilitis, as well as burning or itching.[9,10]

Contact allergy of the oral mucosa, allergic contact stomatitis (ACS), is less common than contact allergy of skin of the lips.[9] A potential explanation regarding this phenomenon involves saliva's cleansing effect, washing away antigens that are presented to the mucosa, where antigen-presenting cells may also be less prevalent.[10] The vascularity of the buccal mucosa also aids in the disper-

Table 1. DIFFERENTIAL DIAGNOSIS OF ALLERGIC CONTACT CHEILITIS[9,10,28,29]

Diagnosis	Clinical Presentation	Comments
Allergic contact cheilitis	Angular cheilitis, dryness, fissuring, edema, crusting; may have effacement of vermillion border	
Irritant contact cheilitis	Angular cheilitis, peri-oral dryness and scaling	"Lip licking" dermatitis, xerostomia (dry mouth)
Actinic cheilitis (solar keratosis)	Hyperkeratosis, erythema, crusting, erosions; may have effacement of vermillion border; background of facial actinic damage; lower lip > upper lip	Often associated with fair-skinned individuals; sunburn, phototoxicity, chronic, premalignant
Atopic dermatitis	Angular cheilitis	
Seborrheic dermatitis	Angular cheilitis	
Perioral dermatitis	Zone of normal skin immediately surrounding vermillion border	
Oral lichen planus or lichenoid oral lesions	May appear erosive	
Perlèche (*C. albicans*)	Angular cheilitis/inflammation; usually bilateral; may have maceration of commissural epithelium	Associated with dentures, diabetes, debilitated individuals, chronic antibiotic use, HIV patients
Infectious cheilitis (Staphylococcal or Streptococcal)	Acute, pustular and fissured cheilitis; usually bilateral	Sick or malnourished children
Secondary syphilis	Split papules	
Herpes simplex	Vesicular	
Aphthous ulcers	Region of complete epidermal loss	Lupus erythematosus
Bullous diseases	Vesicles and bulla	Pemphigus, erythema multiforme
Nutritional deficiency: Vitamin B2 (riboflavin), iron, folate, vitamin B12	Angular stomatitis and/or cheilitis: bilateral or unilateral with mucosal pallor at commissures, followed by fissuring and ulceration. Atrophy of oral epithelium with depapillated; red tongue may be seen.	Eating disorders or a history of total parenteral nutrition (TPN)
Cheilitis glandularis	Swollen, enlarged, everted, exposing superficial puncta of the salivary ducts along the mucosal vermilion border. Possible crusting, nodularity may be felt, and viscous fluid may be expressed from the ductal openings.	Chronic, inflammatory disorder of labial salivary glands; lower lip of adult males is usually affected
Cheilitis granulomatosa (Miescher, Melkersson-Rosenthal syndrome)	Nontender, swelling and enlargement of one or both lips; may feel soft, firm, or nodular on palpation	Chronic, episodic, inflammatory; lymphatic obstruction by granulomatous infiltration; upper lip > lower lip. Lingual, palatal, gingival and buccal involvement also may occur.
Mechanical	Dry, chapped, scaling, fissuring; may have maceration of commissural epithelium	Cold, wind, dental trauma, ill-fitting dentures, prognathism (jaw protrusion); older age
Exfoliative cheilitis	Hyperkeratosis and desquamation; may be hemorrhagic	Often factitious activity, i.e. repetitive biting, picking (self-induced trauma)
Iatrogenic (drugs)	Angular cheilitis and scaling of the lips	Isotretinoin (Accutane)

sal of antigens; however, despite this, the mucosa can become sensitized, with a subsequent inflammatory reaction, most often to dental materials and appliances, such as metals, acrylics fillings, crowns and dentures. Cheilitis and circumoral dermatitis usually accompany primary allergic stomatitis, although stomatitis does not necessarily always accompany primary allergic cheilitis.[10] Of interest, early allergen exposure to the oral mucosa may actually be a means to creating tolerance. For example, it is well documented that wearing metal dental braces prior to nickel exposure (ear piercing) confers a lower risk of developing nickel allergy than the reverse of first piercing then being braced.[11]

The North American Contact Dermatitis Group (NACDG) published their results from 2001 to 2004, showing that, of 196 patients presenting with cheilitis, ACC was responsible for 38.3% of these cases.[9] Of these, 16% had a relevant positive patch test (PPT) to both a chemical from the NACDG series, as well as either a personal product or supplemental allergen, and 20% had a relevant PPT to only a supplemental allergen, demonstrating the need for testing additional allergens and personal products.[9] Likewise, two Italian studies, one by Zoli et al, reported that 18% of 83 patients with cheilitis patch tested from 2001 to 2005 had a PPT to a relevant allergen,[12] while the other by Schena et al found that of 129 patients with cheilitis from 2001 to 2006, 65.1% had possible or probable relevant reactions, 42 of which required an extended series.[13] In the United Kingdom, Strauss

Table 2. TOP ALLERGENS AND SOURCES[9,10]

Category		Allergens	Sources
Flavorings/ Fragrances	Myroxylon Pereirae (Balsam of Peru)*[14]		Dental cement liquids
		Cinnamic aldehyde	Toothpaste[32-34]
	Fragrance Mix[12,14,15]	Cinnamic aldehyde* Cinnamic alcohol* a-amylcinnamic alcohol* Eugenol* Isoeugenol* Geraniol Hydroxycitronellal Oak moss absolute	Toothpastes, mouthwashes, chewing gum, dental impression compounds, cosmetics, perfumes, flavorings
	Essential Oils		Toothpastes and mouthwashes
		Clove Oil (Eugenol[35,36] is main constituent)*	Zinc oxide cement, impression pastes, chewing gum[37]
		Cinnamon oil (cassia oil)*	Toothpaste,[38] bubble gum, lipstick
		Tea tree oil	--
		Anise oil	--
		Menthol[39]	Toothpastes, mouthwashes, cough drops, chewing gum, food, candy, cigarettes, liqueurs, mixed drinks
Metals		Mercury**	Dental amalgam fillings
		Sodium gold thiosulfate	--
		Nickel sulfate[21]	Dentures, nickel-plated dental instruments,[40] bobby pins,[41] jewelry, makeup or lipstick containers[14]
		Potassium dichromate[21]	Dentures
		Cobalt chloride	Pins used with dentures
Acrylic resins[42]		2-hydroxyethyl methacrylate[43]	Acrylic (artificial nails)
		Hydroquinone^	Acrylic dentures
		Benzoyl peroxide^	Acrylic dentures
Preservatives/ Antiseptics		Parabens	Toothpastes and mouthwashes#
		Dichlorophene	Toothpastes and mouthwashes
		Formaldehyde	Thermodent, root canal therapy, nail hardener
		Iodoform	Ribbon packing gauze[44]
		Methyldibromoglutaronitrile/ phenoxyethanol[45]	Personal hygiene products and cosmetics
	Gallates[46]	Octyl gallate	Food, cosmetics
		Propyl gallate	Food, cosmetics
		Lauryl gallate	Food (margarine),[47] cosmetics
		Dodecyl gallate	Food, cosmetics
		Propylene glycol	Pharmaceuticals, foods ("moist" cakes), cosmetics (lipsticks), and personal care products
Foods		Catechol (related to poison ivy oleoresin)	Mango
		Limonene@	Orange peel
Antibacterials		Neomycin sulfate	Creams, ointments
		Bacitracin	Creams, ointments
UV-adsorber		Benzophenone- 3	Lipsticks, sunscreen, dental composite materials
Formaldehyde resin		Tosylamide formaldehyde resin	Nail polish
Stabilizers		Ethylenediamine hydrochloride	Mycolog cream
Vehicle/Emollients		Lanolin alcohol	Ointments, lipsticks
Propolis		Propolis	Lip salves, lozenges
Corticosteroids		Budesonide	Creams and ointments
Rubber accelerators		Mercaptobenzothiazole	Rubber pencil eraser, rubber bands, rubber tips of toothbrushes

*May cross-react with balsam of Peru **May produce urticaria, ectopic, or generalized dermatitis ^Additives in acrylic denture material #May not be listed on the ingredient list of dentrifices @Essential oil

and Orton analyzed patch test data for patients presenting with cheilitis from 1982 to 2001 and found a relevant or possibly relevant PPT in 22%.[14] These same authors also demonstrated the importance of testing personal products, given that 18% of patients with ACC reacted solely to their products. Several relevant sources of reactions were identified, with lipsticks or balms and cosmetics being the most common.[9,12,15,16] Given the prevalence of cosmetic sources, it follows that females account for the great majority of patch tested patients presenting with cheilitis,[9,12-17] and that they are likely to seek medical attention at an earlier date when compared to their male counterparts based on duration of symptoms.[12,15]

Additional relevant sources of allergens in ACC include jewelry, medicaments (corticosteroids and antibacterial creams), oral hygiene products, sunscreens, flavorings in foods and nail varnish.[9,12,15,16] Freeman and Stephens also brought attention to the fact that nickel (in the mouthpiece of a flute) could be a potential source.[16,18]

DIFFERENTIAL DIAGNOSIS

ACC may be difficult to distinguish clinically from many other potential diagnoses (**See Table 1**); therefore, a thorough history is necessary.[10] Not only should an allergen exposure history be obtained, but questions pertaining to ICC, such as lip licking, should be asked as well, as some studies showed ICC as the most common cause of cheilitis.[9,13,16] Conditions such as atopic or seborrheic dermatitis also should be considered. Depending on the clinical presentation, bacterial, fungal or viral cultures can be performed, and potential nutritional deficiency can be addressed. If ACC is still suspected, patch testing is the gold standard for diagnosing allergic contact dermatitis or cheilitis.[4,19]

Perioral dermatitis may have features similar to ACC, but often has a zone of normal skin immediately surrounding the vermillion border compared to allergic cheilitis, where the vermillion is often involved and effaced.[10] Oral lichen planus (LP) or lichenoid oral lesions may be caused by contact allergy to dental materials, particularly those containing metals such as mercury, gold, nickel and chromium.[20,21,22] Therefore, if LP lesions are in proximity to such materials, one's index of suspicion should be raised.[10] In addition, perlèche-like symptoms may occur in previously sensitized individuals who contact nickel or rubber objects at the corners of their mouth. Erosions resembling aphthous ulcers can also be formed from oral contact with nickel objects[23] and have been reported in patients with allergies to balsam of Peru.[24] Sensitivity to constituents of balsam of Peru in soft drinks, liquors and sauces (seasoning) has also been considered as a cause of recurrent aphthous ulcers.[25,26] In fact, ACD to allergens within toothpastes, mouthwashes, teeth whiteners, chewing gum, food, acrylic resin liquid and dentures have all been reported.[27]

TOP ALLERGENS

Results from patch testing patients with cheilitis have been published internationally, listing several allergens as top culprits[9,10,12-17] (**See Table 2**). The NACDG reported fragrance mix as their most common allergen, followed by Myroxylon pereirae (balsam of Peru), nickel sulfate, sodium gold thiosulfate and neomycin sulfate.[9] Fragrance mix was also listed as the most frequent contact allergen by groups in the United Kingdom,[14] Italy[12] and Singapore.[15]

Nickel sulfate was ranked as the third most common allergen by the NACDG,[9] and, notably, as the most common allergen by both Italian groups.[12,13] The primary sources identified were jewelry and lip cosmetics, which highlights the importance of ectopic nickel allergic reactions, already known in relation to eyelid dermatitis,[9] and generates awareness of the possibility of trace amounts of nickel as a pollutant in cosmetic products.[12,30] Moreover, nickel may also be present in makeup or lipstick containers,[9] as well as dietary sources, such as cocoa, dark chocolate, spinach, oysters and red wine.[31]

PRACTICALS OF PATCH TESTING

As mentioned above, patch testing is often necessary to distinguish ACC from other causes of cheilitis, and to identify the relevant allergen(s) responsible. Screening patch test trays are available, which isolate the most common chemicals and offer the provider clues for potential sources. The North American Standard Series includes allergens from several different categories;[48] however, supplemental trays are also available, such as stomatitis/cheilitis/perlèche,[10] dental materials, cosmetics, fragrance/flavors, and specifically, balsam of Peru at some institutions.[49]

The idea behind using supplemental allergens as well is that by including constituents and cross-reactors of the allergen in question, the chance of demonstrating a relevant positive reaction is greater.[50]

Along these same lines, cosmetic products themselves can also be tested "as is." Dental products, however, may require preparation prior to testing.[10] In summation, these chemicals and products may overcome a threshold for reactivity.

PEARLS OF TREATMENT: EVERY DOSE COUNTS

As alluded to in the preface, one may be exposed to and subsequently sensitized to a contact allergen, such as fragrance, for days to years before demonstrating the clinical picture of ACD. With each exposure, there is an increasing risk of reaching a point at which the immune system meets its metaphorical "threshold" and subsequent exposures at this point can lead to elicitation of a cutaneous response, such as cheilitis.[4,51] Just as repeated contact over time led to this immune response, repeated avoidance of the majority of exposures over time will be required to induce remission.

Avoidance of specific allergens in personal care products can prove to be a tedious task; however, there are programs available to aid in this endeavor. Both the Contact Allergen Management Program (CAMP), a service offered through the American Contact Dermatitis Society (ACDS),[52] and the Contact Allergen Replacement Database (CARD), developed by Mayo Clinic,[53] allow for a provider to enter a patient's known contact allergens and produce a "shopping list" of products void of those particular chemicals. The programs also have the ability to exclude cross-reactors.

Some sources, however, require avoidance creativity and finding alternatives. In cheilitis patients, ingestible sources,

such as chewing gum, cough drops, and liqueurs in menthol-allergic patients, margarine in gallate-allergic patients, and peanut butter in nickel-allergic patients,[54] should be given consideration. Educating patients to increase their awareness of sources of allergens and having the patient inform their health and dental professionals of their contact allergens is also important. ■

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Disclosure: Dr. Jacob is the principal investigator for Smartchoice USA PREA-2 trial.

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