

Allergic Skin Disease

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KEYWORDS

- Atopic dermatitis • Contact dermatitis
- Allergic skin disease • Allergy

Key Points: ALLERGIC SKIN DISEASE

- Atopic dermatitis and contact dermatitis are two very common skin disorders which can be associated with significant patient discomfort and morbidity in the peri-surgical time-frame.
- Skin care, anti-inflammatories, anti-infectives, and anti-pruritics are all vital to the successful treatment and prophylaxis of atopic dermatitis.
- Identification of the causative agent and avoidance are the hallmarks of successful treatment for contact dermatitis.
- Flares of allergic skin disease are common following surgery, but can be minimized through proper prophylaxis individualized to each patient.

The skin is the largest immunologic organ in humans, accounting for approximately 15% of our body weight, with a surface area of 1-2 square meters in an adult. Immune dysfunction can affect this massive organ in several ways, with some of the more common being atopic dermatitis, contact dermatitis, urticaria, angioedema, psoriasis, and autoimmune blistering disorders. As surgeons who often violate the skin and mucosa it is vital to understand these disease processes and how they may interact with the expected outcomes of surgical procedures. This review will focus on the two allergic skin diseases which are most common in the world, but the least familiar to Otolaryngologists - atopic dermatitis and contact dermatitis.

ATOPIC DERMATITIS

Atopic dermatitis, also referred to as eczema, is an extremely prevalent chronic inflammatory skin

disease. It affects up to 20% of the pediatric population, making it the most common skin disorder in children. The disease can persist into adulthood, and rarely manifest later in life, affecting 3% to 5% of the adult population. Its prevalence is higher in industrialized nations, and, within these nations, higher in urban than rural regions.¹ In the late 1990s, 2 studies showed the prevalence of atopic dermatitis to be increasing. One involved a questionnaire of Swedish school children (3000 7-year-olds) in both 1979 and 1991. The prevalence of atopic dermatitis more than doubled in that time (7%–18%).² A second study examined 7000 Japanese school children, revealing a doubling of the number of affected children aged 9 to 12 years in a 20-year period, and a fivefold prevalence increase in 18-year-olds in the same time period.³

Seventy percent of patients with atopic dermatitis develop symptoms before the age of 5 years,

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with symptoms frequently present in early infancy. Thirty percent of these patients develop asthma, and 35% develop allergic rhinitis.⁴ It has long been debated whether it is the disorder of atopic dermatitis that predisposes to this presumed worsening and extension of allergic disease. This progression of allergic diatheses has been commonly referred to as the atopic march and led to use of antihistamines in young children with atopic dermatitis to try to prevent the development of these other disease processes. There is no evidence to support this approach, except when specific sensitizations to other antigens are identified.⁵ There are other factors that may predispose to the development of asthma in these patients, particularly filaggrin defects, which are discussed later.

The natural history of atopic dermatitis leads to resolution of disease by early adolescence in 60% of children, although 50% may recur into adulthood. Predictors of persistent disease include early onset, severe early disease, asthma and allergic rhinitis, and family history. Evidence of food and inhalant allergy before the age of 2 years also predicts severe disease.⁶

The cause of atopic dermatitis remains elusive, although many clues have been gained in recent years. There seems to be a role for genetic predisposition, immune responses, epithelial barrier dysfunction, infectious agents, and environmental factors. With regard to genetics, when both parents have atopic dermatitis, there is an 81% chance that the child will have the disease. When only 1 parent is affected, the child may show signs of eczema 59% of the time.⁷ Several suspect genes have been identified, including some coding for components of the immunoglobulin E (IgE) receptor and Th2 cytokines.^{8,9} Perhaps most promising are those mutations that seem to interact with the epithelial barrier of the skin.

The Epithelial Barrier

One of the most important roles performed by the skin is as a barrier between the external environment and our internal milieu. It decreases the permeability to water, allowing decreased evaporation and maintenance of an intact, fluid-filled barrier. It also has antimicrobial and antioxidant effects. Normal skin has an acidic pH, which is inhospitable to colonization by certain bacteria, particularly *Staphylococcus aureus*. The skin is the body's largest immune organ, serving as a site for the initiation of both cellular and humoral immune reactions. Disorders have been identified in atopic dermatitis that can interfere with any or all of these integumentary functions.¹⁰

Filaggrin is a protein normally produced in skin. Its name comes from filament of aggregation integrity of the skin. As skin matures, the cells get smaller until they form the dead stratum corneum, which forms the main barrier between the environment and our immune system. Filaggrin is produced in the granular layer. It is initially formed as profilaggrin, which is broken down into filaggrin and some breakdown products. These products include keratohyaline granules and free amino acids that eventually find their way to the stratum corneum and contribute to the acid mantle, preventing bacterial colonization. The filaggrin then binds to, and is responsible for, keratin aggregation. It induces the cytoskeleton to collapse and form corneocytes. The corneocytes are then cross-linked and form a strong barrier to evaporation.¹¹

Filaggrin mutations have previously been identified in patients with ichthyosis vulgaris, and, more recently, loss-of-function null mutations have been identified in patients with atopic dermatitis. Filaggrin mutations have been associated with early onset of disease and eczema-associated asthma.¹² This association with asthma takes away from the atopic march hypothesis and explains the airway hyperreactivity in terms of a defect in the epithelial lining of the airway. The importance of filaggrin is further highlighted by a study that showed that patients with atopic dermatitis had low filaggrin expression, even if they did not have full loss-of-function mutations.¹³

A loss of filaggrin function or expression leads to a weakening of the epithelial barrier by decreasing the strength of the stratum corneum. This weakening causes excess water evaporation and drying of the skin. In addition, decreased breakdown of profilaggrin ultimately leads to an alkalization of the skin surface, making the environment more hospitable to pathologic bacterial colonization.¹¹

The alkalization of the skin has another effect: upregulation of serine proteases. These important enzymes activate proinflammatory cytokines in the skin. They also lead to production of proteins that decrease integrity and cohesion in the skin, as well as downregulating lipid production, which further weakens the permeability barrier. An acquired or inherited increase in the activity of serine protease may be the inciting event in some cases of atopic dermatitis.¹⁴

Inflammation plays a major role in the pathogenesis of atopic dermatitis. A Th2-predominant reaction is present in acute flares, as shown by the production of interleukin (IL)-13, IL-4, and IL-5. Langerhans cells are hyperactive, overstimulating the T cells. Phosphodiesterase regulation is faulty, causing excessive cytokine production.

There is also a humoral immune response, with increased production of IgE in up to 80% of cases (often caused by staphylococcus toxin superantigens). When a barrier defect is present, cytokine and growth factor production is increased, leading to increased DNA transcription and epidermal hyperplasia, thus accounting for the lichenification that can be seen in many patients with atopic dermatitis. Chemokines are also produced, attracting inflammatory cells and stimulating the production of Th2 cytokines, which has the effect of stimulating further inflammation and decreasing filaggrin production, further damaging the epithelial barrier.¹⁵

The itch-scratch cycle is often described as the root cause of atopic dermatitis, and it is part of the vicious cycle seen in these patients. An example of this cycle might start with alkalinization of the skin by using the wrong soap. This alkalinization then upregulates the serine proteases, which initiate a cellular inflammatory cascade. This inflammation has several effects, including decreased production of filaggrin, which further weakens the epithelial barrier and water evaporates. Mediators of pruritus are also released, causing the patient to scratch. The scratch and water loss further damage the barrier, and the cycle begins again. The best way to break the itch-scratch cycle is to keep the skin hydrated and decrease the inflammatory response, and this forms the backbone of any treatment plan for atopic dermatitis.

Clinical Presentation of Atopic Dermatitis

Patients with atopic dermatitis have dry, itchy, flaky skin. There may be oozing, weeping, and fissuring of the skin. Other features include erythema, excoriation, edema, and lichenification. In infants and young children, the facial and extensor surfaces of the skin are most frequently involved. The diaper area is usually spared; this is probably the best example of the benefit of scratch prevention: the diaper area is spared because the infants cannot get under the diaper to scratch. In older children and adults, the flexural surfaces become more involved. Oozing and weeping may signify a secondary bacterial infection. Dennie-Morgan lines, the folds and wrinkles in the infraorbital skin, may be exaggerated, and the same can apply to palmar creases of the hands. There may be pigmentary changes, with actively involved skin being a little darker than uninvolved skin. As it heals, skin that was involved may be lighter because of a decreased change with tanning. Hyperkeratosis pilaris, an accentuation of the hair follicles, is common on the face and upper arms.

Patients with atopic dermatitis experience their disease in different ways, but one thing is universal: pruritus. They can usually tell a flare is coming by the onset of the itch. The initial insult to the skin may not have been noticed. The flares may involve multiple sites or be isolated to 1 region, and patients can flare twice a month or twice per year. Each patient with atopic dermatitis is different and their disease severity must be graded and treated appropriately.

Management of Atopic Dermatitis

Skin care

Hydration of the skin is the mainstay of treatment of atopic dermatitis, and simple baths are the first step. Baths have been a controversial subject in the past, with some believing that bathing dries the skin. This statement is true because of the phenomenon of wet evaporation, especially with hot water. However, bathing hydrates the skin; patients should not wait long enough for the water to evaporate. This warning has led to the 3-minute rule, which states that an emollient should be applied to the skin within 3 minutes of exiting the bath.¹⁶

Baths are recommended for patients with atopic dermatitis, usually daily, with only gentle, nonalkalinizing soaps. Patients should avoid irritating oils and bath salts and never use a scrub brush or wash cloth, which might irritate the skin. After the bath, they should blot dry or drip dry before applying any medication and emollient within 3 minutes.

Emollients are as important as the baths. These patients have a deficiency in the barrier that keeps moisture in the skin, so moisture must be constantly replaced. This moisturizing should be in the form of an ointment or cream. Lotions should be avoided because they tend to have large amounts of water in them that evaporates and can dry the skin. Ointments are helpful for thick, fissured, lichenified skin, but they are aesthetically undesirable because of their greasy appearance. Many use a cream during the day, but an ointment at night, for this reason. There are several gentle emollients on the market.

When a flare is particularly severe, hydration may need to be more aggressive, and wet wraps may be the solution. After the bath, an antiinflammatory medication is applied, followed by an emollient. The affected areas are then covered with soft bandages that are damp. These damp bandages are then covered again by dry ones. Wet wraps not only increase hydration, but increase steroid penetration, serve as a scratch barrier, and allow rapid healing of excoriated lesions.¹⁶

All skin irritants should be avoided in the patient with atopic dermatitis. These irritants include soaps, detergents, and moisturizers that are alkalizing. Laundry detergents should be liquid and mild, with an extra rinse cycle to ensure their complete removal from clothing. Heat and perspiration can irritate the skin and sunburn can be devastating. Use of a good sunscreen is a vital part of any atopic dermatitis treatment plan. Physical barriers are better than chemical, so zinc oxide or titanium oxide should be preferred. Occlusive and scratchy clothing should also be avoided. Patients do best with loose-fitting cotton, silk, and cotton blends.

Antiinflammatory medication

After hydration, the next important step in the treatment of atopic dermatitis is stopping the inflammation, and this is most often accomplished through the use of topical corticosteroids. Topical corticosteroids are safe and effective when used correctly. Possible side effects of topical corticosteroids include atrophy of the skin, telangiectasia development, dyspigmentation, perioral dermatitis, and striae. It is important for the provider to be familiar with the various strengths of topical corticosteroids available. Low-strength preparations (eg, hydrocortisone) are not effective for moderate to severe disease, and it would not be prudent to prescribe an ultra-high-dose formulation (eg, clobetasol) to treat the face where skin thinning and telangiectasias are a concern. Ointments generally have a higher potency than creams. Fluticasone propionate and mometasone furoate are the only preparations that have proven efficacy against atopic dermatitis in daily dosing. The ointment formulations of these are considered high potency, whereas the creams are midpotency.¹⁷

An alternative for topical antiinflammatory treatment in these patients is a calcineurin inhibitor, which are nonsteroidal topical immunomodulators, and the 2 available preparations are tacrolimus and pimecrolimus. When a T cell is presented with an antigen, calcium production is increased, causing calcineurin and calmodulin to bind intracellularly, ultimately leading to increased Th1 cytokine production.

By blocking calcineurin, these medications decrease cytokine production and block the inflammatory cascade. They have proved to be efficacious in mild to moderate atopic dermatitis.¹⁸

The advantage of topical calcineurin inhibitors is that they are steroid sparing and do not have the typical side effects associated with topical corticosteroids. They are safe to use on the face and the thin skinfolds of the body. There may be a transient

burning or stinging with the initial applications, but they are typically well tolerated. The US Food and Drug Administration (FDA) has placed a black-box warning on these agents because of an increased lymphoma risk in animal studies, and perhaps in humans on systemic doses. There is no scientific evidence to support an increased risk of malignancy caused by topical treatment with calcineurin inhibitors.¹⁹ These agents continue to be used routinely, but are reserved for second-line therapy, as recommended by the FDA.

Secondary infection

S aureus colonization is common in atopic dermatitis, with infections becoming evident in up to 80% of patients. Involved skin starts crusting, with pustules consistent with impetigo and folliculitis. Inflammatory cells are then activated, which leads to increased pruritus, scratching, and initiation of the whole vicious cycle, which continues to exacerbate and spread not only the atopic dermatitis flare but the infection as well. In addition, the staphylococcus toxins serve as superantigens, activating the immune system nonspecifically and greatly increasing the production of IgE. Up to 80% of the increased IgE in patients with atopic dermatitis is directed at the staphylococcus exotoxin.²⁰

Treatment of acute infection usually involves parenteral antibiotics. Topical antibiotics can be used, but those preparations often contain preservatives and other substances that can exacerbate atopic dermatitis, or even cause a contact dermatitis. The most commonly used antibiotics are cefadroxil, cephalixin, cefdinir, trimethoprim/sulfa, and tetracycline.²¹ Bleach baths are also effective in both active skin infection and prevention of colonization. Bleach is sodium hypochlorite, which has broad antimicrobial activity because of its action of oxidizing bacteria. There is no known resistance and it is nontoxic to human skin at dilute concentrations, similar to a chlorinated swimming pool. One-eighth to one-quarter of a cup of bleach is added to a full tub of water, and a typical bath is taken, lasting approximately 10 minutes. Twice-weekly bleach baths may decrease the likelihood of acute infection. One study has shown a significant decrease in the severity of atopic dermatitis when twice-weekly bleach baths are combined with intranasal mupirocin.²²

Other infections can be devastating to the patient with atopic dermatitis and must be in the differential any time a change to the typical appearance of affected skin is identified.²³ Eczema herpeticum is characterized by ulcerative lesions caused by the herpes virus. A Tzanck smear can confirm the diagnosis and treatment is with parenteral acyclovir.

Tinea infections have an advancing border, with central clearing. A KOH prep can confirm the diagnosis and treatment involves antifungals. Molluscum contagiosum can also complicate atopic dermatitis. This condition is characterized by papules with central vesiculation. Treatment is difficult, because most of the typical antiwart medications can exacerbate the skin disease.

Allergy role in atopic dermatitis

Allergy has long been suspected to play a role in atopic dermatitis, and it seems that food allergy can be a major contributor to the disease. Up to 37% of children less than 5 years of age with moderate to severe atopic dermatitis have IgE-mediated food allergy.²⁴ It is still unclear whether exposure to certain suspect foods can exacerbate disease. Several studies have endeavored to show improvement in atopic dermatitis when avoidance of identified allergenic foods is practiced, but there is little evidence to support the hypothesis.²⁵ Some studies did show a significant decrease in pruritus when patients allergic to egg practiced strict avoidance.^{26–28} When foods are removed from the diet and tolerance develops, it seems they can be safely returned to the diet without exacerbation of skin disease.²⁹ When standard treatment of atopic dermatitis fails to lead to improvement, testing and treatment of food allergies should be considered. Ninety percent of the positive food reactions in these patients are to 1 or more of 6 foods:

1. Egg
2. Nut
3. Milk
4. Soy
5. Wheat
6. Fish.

Sensitization to aeroallergens may be seen in patients with atopic dermatitis, although there does not seem to be a significantly higher prevalence than in the general population. However, aeroallergens can exacerbate atopic dermatitis either through inhalation or direct contact. The most important allergens involved are dust mite, animal dander, and pollens. The role of dust mite is supported by patch tests, avoidance studies, and high IgE titers to mite antigens in a large proportion of patients with atopic dermatitis.³⁰ The positive effect of house dust mite avoidance has been shown in several studies.³¹ A work-up for inhalant allergy should only be performed in patients with atopic dermatitis if the history otherwise suggests aeroallergen sensitization. Patch testing to common aeroallergens, especially dust mite, should be considered in refractory cases.

Pruritus

Controlling the pruritus is the most difficult aspect of treatment of atopic dermatitis. If patients can stop scratching, the epithelial barrier has time to heal and recovery is much quicker and complete. Scratching also promotes secondary infection. The best tools for pruritus at this time are the first-generation antihistamines. These medications are not good at stopping the itch, but the sedative qualities are effective. Preparations chosen for this task are typically diphenhydramine, hydroxyzine, or doxepine, but they need to be used in higher doses than are typically seen for allergic rhinitis. Driving should not be allowed while taking these medications at these dosages. There are some topical preparations available for itch relief, the most popular being pramoxine for patients with atopic dermatitis. Topical diphenhydramine and doxepine should be avoided in these patients because they are strong sensitizers. Second-generation, nonsedating antihistamines seem to have little or no value in treating these patients.³²

Systemic therapy for atopic dermatitis

Phototherapy and photochemotherapy have been used for several decades in patients with difficult-to-treat atopic dermatitis. It has been repeatedly shown to significantly induce therapeutic beneficial effects at a low cost. Currently, it is most often used as part of a rotational treatment regimen to avoid long-term adverse effects of other medications.³³

There are systemic options available for atopic dermatitis, but they should be reserved for difficult cases in which all of the treatment recommendations discussed earlier have failed. Systemic corticosteroids should only be used in crisis situations. They work well to treat a severe acute flare, but their use is also associated with a strong rebound effect, often leaving the patient with worse disease than when they began. Other systemic immunomodulators have been used with some success, including cyclosporine A, mycophenolate mofetil, and azathioprine. Interferon γ , infliximab, efalizumab, and omalizumab have also been used in isolated cases, with some success.¹

Proactive treatment of atopic dermatitis

Every patient with atopic dermatitis should have an action plan to outline the proper treatment of their disease, whether all skin is uninvolved, they have a mild flare, or a severe outbreak. The action plan should be based on the general supportive care involving skin hydration and barrier therapy (eg, emollients, baths) along with avoidance of irritants. It should include the topical antiinflammatory to be used in the event of a mild disease

flare (perhaps a low-dose steroid such as 2.5% hydrocortisone), as well as the choice for a more severe flare (eg, 0.1% mometasone). When the higher-dose steroid is needed, the plan should include instructions on tapering to a lower-dose topical corticosteroid before discontinuing its use, thereby avoiding a rebound flare.

Treatment between flares has proved to be beneficial for patients with atopic dermatitis. They should always avoid skin irritants and practice good skin hydration, but the addition of an antiinflammatory has proved beneficial as well. One study of 376 patients with moderate to severe atopic dermatitis proved that those treated with a twice-weekly steroid ointment (fluticasone) were 5.8 times less likely to flare than controls.³⁴ In another study, 383 patients were evaluated for the effectiveness of tacrolimus, used proactively 3 times per week. Patients on tacrolimus maintenance had significantly fewer disease relapse days and more flare-free days than controls.³⁵

Atopic Dermatitis and the Rhinoplasty Patient

Any surgical procedure puts patients with atopic dermatitis at risk for an acute flare of their disease. This risk must be weighed against the potential benefits of the surgery when making a decision to proceed. There have been no controlled studies examining any protocol to prevent disease activation in these patients. The following recommendations are based on the science of the disease process and the known benefits of standard therapy, along with anecdotal reports from physicians who have dealt with this issue in the past.

Patients should be instructed to maximize their routine skin maintenance during the week leading up to the surgery, behaving as if they had a flare. This strategy may include increased use of emollient ointments following daily short baths. Two bleach baths during this week may be beneficial as well. Use of antiinflammatory medication in this setting is controversial, but many recommend 2 applications of a low-dose topical steroid (no stronger on the face) or 3 applications of a calcineurin inhibitor, if this is what the patient has used in the past. Some go so far as to use a daily topical antiinflammatory leading up to the surgery, being cognizant of the potential effects on wound healing.

At the time of surgery, the skin prep must be as gentle as possible. The friction associated with the usual perioperative cleansing is enough to initiate a flare on its own. The antiseptic used should also be carefully selected. Chlorhexidine and betadine may be safe because of their slightly

acidic pHs, but betadine usually contains alcohol, which may be more drying. Regardless of which substance is used, it must be applied in a gentle manner, with a nonabrasive sponge. When the surgery is complete, a similar sponge can be used to gently clean the prep area, or it may be left in place for patients to wash away at home with their soap of choice. It would be wise to apply an emollient to the entire surgical field at the end of the case. Antibiotic ointment can be used if the patient has not had problems with them in the past.

Patients should be instructed to continue their increased skin care for 1 more week, along with gentle wound care. A topical steroid or calcineurin inhibitor can also be used in a similar fashion to the week before surgery. If a flare does occur, the patient should be prepared and treat it as they would any other exacerbation of their disease.

CONTACT DERMATITIS

Contact dermatitis is a common inflammatory skin condition, characterized by erythema and edema occurring after contact with a foreign substance. The 12-month prevalence of occupational contact dermatitis has been shown to be 1700 cases per 10,000 workers.³⁶ Natural resources and mining, manufacturing, and health services have the highest rates of affected individuals.³⁷ Contact dermatitis ranks second only to traumatic injury as the most common type of occupational disease.³⁸ However, the disease is more than an occupational entity. It affects individuals from all walks of life, with sensitizations and reactions to everyday substances causing extreme discomfort and disrupting the quality of life for hundreds of thousands of patients.

It may be categorized as either allergic contact dermatitis, accounting for 20% of cases, or irritant contact dermatitis seen in the other 80%. There are many factors that affect the response in contact dermatitis, but at the heart of the issue are 85,000 chemicals, more than 3700 of which have been identified as contact allergens. Many allergens can serve as irritants and chemical irritants can also produce sensitizing allergic reactions, so differentiating between the 2 types can be difficult.³⁹

Contact dermatitis usually manifests as erythema and scaling with well-demarcated borders. In the irritant form of the disease, the skin lesions are often painful, and may be described as burning or stinging. The demarcation in these cases is often sharp. In contrast, the skin lesions in allergic contact dermatitis can be extremely pruritic; the itch is usually the predominant feature. The edges

of the skin disruption can be less distinct in these patients. Irritant contact dermatitis is most often seen on the hands, but can occur in other regions (eg, lips with excessive lip licking, diaper area caused by irritant diaper dermatitis). Allergic contact dermatitis can occur anywhere. These 2 forms of disease can also overlap.

Irritant contact dermatitis is a result of skin injury, direct cytotoxic effects, or cutaneous inflammation from direct contact with an irritant. This inflammation is a more recent discovery, involving upregulation and recruitment of chemokine genes, regulated by T-cell effector cytokines. Allergic contact dermatitis is caused by a type IV, delayed hypersensitivity reaction. This reaction requires prior sensitization to the involved substance, and leads to the reaction being delayed by 48 hours.

The diagnosis of contact dermatitis is most often made through history and physical examination. The location of the lesions, combined with a history of exposures in that area in the past few days, can often be enough to lead to an avoidance trial (eg, earlobes from nickel-containing earrings, area of the skin treated with a topical antibiotic). When the diagnosis is in question or the avoidance trial is not successful, patch testing can be performed. Patch testing is the only practical, scientific, and objective method for the diagnosis of allergic contact dermatitis and is discussed further later.

Testing for Contact Dermatitis

Patch testing involves the application of potential allergenic substances to the surface of the skin, leaving them in place for 48 hours to assess for delayed-type hypersensitivity reactions to the allergens. Ninety percent of allergists currently use a commercially available patch test known as the TRUE test (thin-layered rapid-use epicutaneous test) (Allerderm, Phoenix, AZ, USA). This test consists of 3 self-adhering strips, containing 29 antigens, covering some of the most common causes of allergic contact dermatitis. The strips are applied to the upper back and removed after 48 hours. The first reading is done 30 minutes later. A second reading is required to detect reactions that may be more delayed, and this is done at 72 or 96 hours, or even a week later. Thirty percent of negative tests at 48 hours may be positive on delayed readings. Patients are instructed to report any positive reactions to their provider for up to 3 weeks. Neomycin and corticosteroid reactions may not be apparent until 7 days after application. A reaction that is positive at the immediate reading but negative at 72 hours is likely an irritant, not an allergen.⁴⁰

Allergens not found in the TRUE test panel can frequently cause allergic contact dermatitis. The North American Contact Dermatitis Group has ranked the most common allergens as causative agents for allergic contact dermatitis. This list includes at least 3 substances that are not included in the TRUE panel: gold, bacitracin, and methyl dibromoglutaronitrile (a common component of cosmetics). The North American Contact Dermatitis Group has compiled a series of 65 to 70 antigens that they recommend as an optimal panel for patch testing. Use of this panel would be less likely to miss a cause of allergic contact dermatitis, but is more labor intensive, requiring filling of each individual well with the antigen to be tested.⁴¹

Standardized test panels are available from several manufacturers. Kits are also available for specific exposure patterns, such as hairdressers, shoes, plants, photoallergens, vehicles, metals, antibiotics, and corticosteroids. When a particular personal hygiene product is suspected, the cosmetic industry may supply blind antigens for testing. However, they will not tell you what they are unless you have a positive result. Personal products can also be applied to the wells in a patch test and tested undiluted or in diluted concentrations.⁴⁰

Patch test results are generally reported as weak positive with erythema, infiltration, and possibly papules; strong positive with erythema, infiltration, papules, and vesicles; or extreme positive with bullae and ulcerations. If a result is marginal, it is prudent to wait until 96 hours. If the intensity and/or pruritus worsen, it is likely allergic. Irritant substances can cause false-positives, again making the delayed reading important. Patch test results can be confirmed or denied through an open application test in which the suspect personal product is applied to the antecubital fossa 2 times per day for 5 to 7 days. Absence of a reaction makes contact dermatitis from this substance unlikely.

Common Contact Allergens

Urushiol

One of the most common causes of allergic contact dermatitis, and the easiest to diagnose, is exposure to urushiol, a substance in the sap of *Rhus* plants (poison ivy, oak, and sumac). *Rhus* plants can brush against the skin, causing linear streaks of erythema and vesicles. This type of contact dermatitis often covers large areas of the body because the urushiol can be spread to other regions, including the face and genitals, by direct contact. More than 70% of people exposed to these plants become sensitized.⁴²

Topical medications

Allergic contact dermatitis to topical medication is common. Neomycin is the most frequently encountered culprit, being the third most common overall contact allergen in North America. Its incidence seems to be increasing and cross-sensitivity is frequently seen with gentamycin, kanamycin, streptomycin, and tobramycin. The only safe topical antibiotic for use in these patients is mupirocin. Neomycin contact dermatitis accounts for more than 10% of shoe-induced dermatitis. The reason seems to relate to the absorption of neomycin into the leather and fabric of shoes. In these cases, an abrasion on the foot treated with neomycin allows the agent to seep into the shoes. When the shoes are worn again a year later, the contactant is still present and a reaction occurs. These shoes must be discarded, but the problem does not arise in all shoe leather.⁴³

Topical corticosteroids were voted the 2005 Allergen of the Year by the North American Contact Dermatitis Group. The prevalence of reactions to these agents seems to be increasing, but clinicians may be better at detecting them because of increased awareness, an expanded market, and improved patch testing procedures. Allergic contact dermatitis to corticosteroids should be considered in stasis ulcers and chronic eczema, when dermatitis fails to respond to corticosteroids, and when dermatitis worsens with treatment. There are structural subtypes of corticosteroids based on immune recognition sites, and a reaction to one of these classes does not preclude use of one of the others. For example, hydrocortisone, a class A steroid with a C17 short-chain ester does not cross-react with betamethasone, a class C steroid with a C16 methyl group. Steroids are most often patch tested using tixocortol (class A), budesonide (class B and D), and the patient's own commercial steroid preparation; this accounts for up 91% of corticosteroid allergy.⁴⁴ Other panels are available for more extensive testing, if desired.

Topical anesthetics, including benzocaine, tetracaine, and dibucaine, can be causative in allergic contact dermatitis. Thimerosal, a preservative in many topical medications, vaccines, cosmetics, and contact lens solutions, can also be an allergen. Topical quinolones have also been associated with contact dermatitis.³⁸

Rubber

Allergic contact dermatitis to rubber and its components is a complex problem. Mercaptobenzothiazole, thiuram mix, black rubber mix, carba mix, and mercapto mix have all been studied in routine patch testing. Most rubber-sensitive

individuals are positive to several of these antigens and cross-sensitization is common.⁴⁵ This type of contact allergy is a large component of latex allergy, but does not tell the entire story. There are components of latex that are not available for testing, making the diagnosis more difficult.

Cosmetics

There are more than 2800 fragrance ingredients in a database maintained by the Research Institute for Fragrance Materials, Inc. One-hundred of these are known allergens. Any given fragrance is a complex substance containing hundreds of different chemicals, and these are the most common cause of allergic contact dermatitis caused by cosmetics. Balsam of Peru and Fragrance Mix" are components of the TRUE test that can diagnose many of these patients. When a fragrance allergen is identified, it is important to educate the patient on the term unscented used in the cosmetic industry. This term erroneously suggests that a product does not contain a fragrance, when a masking fragrance is present. In contrast, fragrance-free products are generally acceptable for the allergic patient. Products that are fragrance free with botanic extracts are not safe for use in this population.⁴⁶ Other components of cosmetics can act as allergens as well. These components include the numerous preservatives, vehicles, and additives used by the industry. In the TRUE test, these are tested as quarternium 15, imidazolinyl urea, diazolidinyl urea, formaldehyde, paraben, and wool alcohols. Although this is a good, representative example, many contactants can still be missed, simply because there are so many.⁴⁶

p-Phenylenediamine is the main contact allergen identified in hair products, including dyes and permanents. It is also present in black henna used for tattooing. It is a common source of allergic contact dermatitis in the hair care industry. *p*-Phenylenediamine does not cause a reaction if it is fully oxidized, which means that patients with this particular allergy cannot apply hair dye, but they can cut the hair of someone who has had their hair dyed previously. Preparations used for hair permanents work by continually leeching from the hair to which it has been applied. For this reason, the same patient should not cut the hair of someone who has had a permanent in the recent past.⁴⁷

Metals

Nickel was the Contact Allergen of the Year for 2008, according to the North American Contact Dermatitis Group, with an increasing incidence in the United States (10.5% from 1985 to 1990,

18% in 2004). Body piercing is the most common cause, and ear piercing is thought to account for the high sensitivity documented in children. When school-aged girls are patch tested, those with their ears pierced are sensitive to nickel 13% of the time, whereas only 1% of those without pierced ears are sensitive. All metal pins used for ear piercing release nickel in varying amounts, leading several European nations to legislate the amount of nickel allowed in these piercing instruments. Early results show a significant decrease in the prevalence of nickel allergy in young women after the law was instituted.⁴⁸

There is evidence to support a contribution of dietary nickel to vesicular hand eczema, as well as systemic contact dermatitis.⁴⁹ A meta-analysis of systemic cases revealed that approximately 1% of patients with nickel allergy have systemic reactions to the nickel content of a normal diet. Ten percent more react if the exposure is in the range of 0.55 AH to 0.89 AH mg, greater than the normal diet, but easily reached if foods with higher nickel content are eaten. These foods include cocoa, lentil, soybean, fig, cashews, and raspberries.⁵⁰

The use of nickel in biomedical devices, especially in joint prostheses and endovascular stents, has led to increased concerns about the safety of these implants in patients with suspected nickel sensitization. Reports of these types of allergy have led to great variability in the management of these cases. There are no large, evidence-based, prospective studies examining this issue. Some surgeons and cardiologists refer any patient, with even the slightest suspicion of contact dermatitis, for patch testing. A positive test result might lead to the selection of a more expensive and less optimal implant. With regard to endovascular stenting, one study examined coronary in-stent restenosis 6 months after stainless steel stent placement and patch tested 2 months after angioplasty. There were 11 positive patch test reactions in 10 of the patients (8%). All 10 patients with a positive patch test reaction to metal (7 nickel, 4 molybdenum) had in-stent restenosis. This restenosis rate was significantly higher than the nonallergic patients. The clinical history was not predictive of a positive patch test.⁵¹ In another prospective study of 174 stented patients, those with in-stent restenosis had a significantly higher prevalence of positive patch tests to metal (nickel and manganese).⁵² Currently, the evidence for complications caused by nickel allergy is weak, with rare proven cases reported in the literature. The need for patch testing is controversial and the results are poorly reliable in predicting or confirming an implant reaction. Although a negative test might be reassuring, if

a positive test is achieved, the implant must be removed.

Although mostly used in jewelry, gold is also an antiinflammatory medication, is used in the electroplating industry, and is part of many dental appliances. Allergic contact dermatitis from this metal has become common, with 9.5% of 4101 patch-tested individuals having a positive reaction.⁵³ The most common sites of involvement are the hands, the face, and the eyelids. The involvement of facial and eyelid skin is intriguing, because gold is not often in direct contact with these areas. It seems that titanium dioxide, found in many cosmetics, adsorbs gold released from jewelry, spreading it across the face.⁵⁴

Treatment

The primary treatment of any contact dermatitis is identification and avoidance of contact with allergens and irritants. Although history and location of the skin lesions are helpful, there is no substitute for patch testing. In a study evaluating the differences between patch-tested and non-patch-tested patients with allergic contact dermatitis, relief of symptoms was achieved an average of 143 days sooner in those who had undergone a patch test.⁵⁵ Once the causative agents are identified, the patient should be provided with instructions detailing the potential sources of the antigen and synonyms by which they may be known. Alternatives and substitutions may be available for any particular antigen, and these are available through the Contact Allergen Replacement Database maintained by the American Contact Dermatitis Society. Simple measures include covering nickel-plated objects (eg, snap-on jeans), washing formaldehyde-containing clothes, and using gloves or other barriers when handling certain chemicals. For nickel-sensitive patients, the widely available dimethylglyoxime swab test can be used on any substance to detect the presence of this sensitized metal.

Supportive care should be offered for relief of pruritus. This care may include cold compresses with water or saline, aluminum subacetate (Burrow solution), calamine, and colloidal oatmeal baths. Excessive washing of the involved areas should be avoided and use of good, gentle emollients, as described earlier for atopic dermatitis, should be considered. An oral, first-generation antihistamine may also be useful against the itch, mostly through its sedating effects.

A topical corticosteroid is the first line-treatment of mild to moderate allergic contact dermatitis, but more severe presentations frequently require systemic corticosteroids. Calcineurin inhibitors

have been tried for these patients, but their efficacy in contact dermatitis has not been established. There seems to be some benefit in chronic contact dermatitis of the hands and feet, but further investigation seems necessary.⁵⁶

Contact Dermatitis and Rhinoplasty

A careful history of contactant allergy should be obtained in any patient being considered for surgery. The surgeon should be mindful of any evidence of dermatitis on the face, eyelids, ear lobes, and hands. Often, patients have been living with these chronic rashes for so long that they neglect to mention them or seek intervention. If a dermatitis is identified, further history might help suggest whether it is a contact dermatitis, as opposed to atopic dermatitis, dishydrosis, or even psoriasis. If contact dermatitis is suspected, patch testing is warranted.

In patients with known allergic contact dermatitis, some adjustments may need to be made to the surgical or in-office practice. Topical antibiotics must be carefully selected in patients with contact allergy. Often, the culprit is neomycin, which can cross-react with many other topical preparations. In these cases, mupirocin should be considered. Nickel allergy is not an absolute contraindication to metal implants, but alternatives should be considered. Resins present in adhesives may cause contact dermatitis to tape. In addition, practice caution when suggesting skin products for these patients with possible allergies to some of the fragrances, preservatives, and additives used in their manufacture.

SUMMARY

Atopic dermatitis and contact dermatitis are extremely prevalent allergic diseases of the skin that can be devastating to the patient, with symptoms including severe pruritus, pain, and cosmetically unappealing inflammation of the skin. Although the disease processes do not affect the outcome of surgery, the procedures may trigger a relapse of disease, severely affecting quality of life and adversely affecting recovery. Through knowledge of the pathophysiology of atopic dermatitis and the potential causative agents in allergic contact dermatitis, the surgeon can avoid exacerbation of preexisting skin inflammation and assist with treatment if a flare does occur.

REFERENCES

1. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol* 2006;118(1):152–69.
2. Aberg N, Hesselmar B, Aberg B, et al. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995;25(9):815–9.
3. Sugiura H, Umemoto N, Deguchi H, et al. Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago. *Acta Derm Venereol* 1998;78(4):293–4.
4. Williams HC. Epidemiology of atopic dermatitis. *Clin Exp Dermatol* 2000;25(7):522–9.
5. Wahn U. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. *Early Treatment of the Atopic Child. Pediatr Allergy Immunol* 1998;9(3):116–24.
6. Lammintausta K, Kalimo K, Raitala R, et al. Prognosis of atopic dermatitis. A prospective study in early adulthood. *Int J Dermatol* 1991;30(8):563–8.
7. Uehara M, Kimura C. Descendant family history of atopic dermatitis. *Acta Derm Venereol* 1993;73(1):62–3.
8. Cox HE, Moffatt MF, Faux JA, et al. Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 1998;138(1):182–7.
9. Forrest S, Dunn K, Elliott K, et al. Identifying genes predisposing to atopic eczema. *J Allergy Clin Immunol* 1999;104(5):1066–70.
10. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;121(6):1337–43.
11. O'Regan GM, Irvine AD. The role of filaggrin in the atopic diathesis. *Clin Exp Allergy* 2010;40(7):965–72.
12. Baurecht H, Irvine AD, Novak N, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol* 2007;120(6):1406–12.
13. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2009;124(3 Suppl 2):R7–12.
14. Hachem JP, Man MQ, Crumrine D, et al. Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. *J Invest Dermatol* 2005;125(3):510–20.
15. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358(14):1483–94.
16. Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association

- "Administrative Regulations for Evidence-Based Clinical Practice Guidelines". *J Am Acad Dermatol* 2004;50(3):391–404.
17. Boguniewicz M, Eichenfield LF, Hultsch T. Current management of atopic dermatitis and interruption of the atopic march. *J Allergy Clin Immunol* 2003; 112(Suppl 6):S140–50.
 18. El-Batawy MM, Bosseila MA, Mashaly HM, et al. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Sci* 2009;54(2):76–87.
 19. Thaci D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. *Clin Dermatol* 2010;28(1):52–6.
 20. Macias ES, Pereira FA, Rietkerk W, et al. Superantigens in dermatology. *J Am Acad Dermatol* 2011; 64(3):455–72 [quiz: 473–4].
 21. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, et al. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol* 2010;163(1):12–26.
 22. Huang JT, Abrams M, Tlougan B, et al. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics* 2009;123(5):e808–14.
 23. Lipozencic J, Wolf R. Atopic dermatitis: an update and review of the literature. *Dermatol Clin* 2007; 25(4):605–12, x.
 24. Eigenmann PA, Sicherer SH, Borkowski TA, et al. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; 101(3):E8.
 25. Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for improving established atopic eczema in adults and children: systematic review. *Allergy* 2009;64(2):258–64.
 26. Atherton DJ, Sewell M, Soothill JF, et al. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; 1(8061):401–3.
 27. Agata H, Kondo N, Fukutomi O, et al. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993;91(2): 668–79.
 28. Lever R, MacDonald C, Waugh P, et al. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998;9(1):13–9.
 29. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(Suppl 6):S1–58.
 30. Platts-Mills TA, Vervloet D, Thomas WR, et al. Indoor allergens and asthma: report of the Third International Workshop. *J Allergy Clin Immunol* 1997;100(6 Pt 1):S2–24.
 31. Tan BB, Weald D, Strickland I, et al. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996;347 (8993):15–8.
 32. Wahlgren CF, Hagermark O, Bergstrom R. The anti-pruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br J Dermatol* 1990; 122(4):545–51.
 33. Byun HJ, Lee HI, Kim B, et al. Full-spectrum light phototherapy for atopic dermatitis. *Int J Dermatol* 2011;50(1):94–101.
 34. Berth-Jones J, Damstra RJ, Golsch S, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003;326(7403):1367.
 35. Breneman D, Fleischer AB Jr, Abramovits W, et al. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. *J Am Acad Dermatol* 2008;58(6):990–9.
 36. Behrens V, Seligman P, Cameron L, et al. The prevalence of back pain, hand discomfort, and dermatitis in the US working population. *Am J Public Health* 1994;84(11):1780–5.
 37. Workplace injuries and illnesses. Washington, DC: US Department of Labor; 2009 (05/2011).
 38. American Academy of Allergy Asthma and Immunology, American College of Allergy Asthma and Immunology. Contact dermatitis: a practice parameter. *Ann Allergy Asthma Immunol* 2006;97(3 Suppl 2): S1–38.
 39. Marks J, Elsner P, Deleo V. Contact and occupational dermatology. St Louis (MO): Mosby; 2002.
 40. Fonacier LS, Dreskin SC, Leung DY. Allergic skin diseases. *J Allergy Clin Immunol* 2010;125(2 Suppl 2): S138–49.
 41. Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. *Dermatitis* 2009;20(3):149–60.
 42. Wolf K, Johnson RA, editors. Fitzpatrick's color atlas and synopsis of clinical dermatology. New York: McGraw-Hill; 2009.
 43. Gehrig KA, Warshaw EM. Allergic contact dermatitis to topical antibiotics: epidemiology, responsible allergens, and management. *J Am Acad Dermatol* 2008;58(1):1–21.
 44. Bjarnason B, Flosadottir E, Fischer T. Assessment of budesonide patch tests. *Contact Dermatitis* 1999; 41(4):211–7.
 45. Bendewald MJ, Farmer SA, Davis MD. An 8-year retrospective review of patch testing with rubber allergens: the Mayo Clinic experience. *Dermatitis* 2010;21(1):33–40.

46. Castanedo-Tardan MP, Zug KA. Patterns of cosmetic contact allergy. *Dermatol Clin* 2009;27(3): 265–80, vi.
47. O'Connell RL, White IR, Mc Fadden JP, et al. Hair-dressers with dermatitis should always be patch tested regardless of atopy status. *Contact Dermatitis* 2010;62(3):177–81.
48. Schram SE, Warshaw EM, Laumann A. Nickel hypersensitivity: a clinical review and call to action. *Int J Dermatol* 2010;49(2):115–25.
49. Kornik R, Zug KA. Nickel. *Dermatitis* 2008;19(1):3–8.
50. Jensen CS, Menne T, Johansen JD. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis* 2006;54(2):79–86.
51. Koster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000;356(9245):1895–7.
52. Iijima R, Ikari Y, Amiya E, et al. The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol* 2005;104(3):319–25.
53. Fowler J Jr, Taylor J, Storrs F, et al. Gold allergy in North America. *Am J Contact Dermat* 2001;12(1):3–5.
54. Ehrlich A, Belsito DV. Allergic contact dermatitis to gold. *Cutis* 2000;65(5):323–6.
55. Rajagopalan R, Kallal JE, Fowler JF Jr, et al. A retrospective evaluation of patch testing in patients diagnosed with allergic contact dermatitis. *Cutis* 1996;57(5):360–4.
56. Wollina U. The role of topical calcineurin inhibitors for skin diseases other than atopic dermatitis. *Am J Clin Dermatol* 2007;8(3):157–73.