Skin Conditions

Do your symptoms include

- Itchy skin
- Dry skin
- Eczema (atopic dermatitis)
- Hives
- Swelling reactions
- Drug reactions
- Contact reactions to metal, poison ivy, or chemicals

Our allergists can help identify the cause and treat the symptoms of various skin conditions. Here’s an in-depth tutorial for your research.

Eczema

Introduction: Eczema

Atopic dermatitis (AD), often termed “eczema”, is a chronic pruritic skin condition that affects about 10-20% of children and about 2-3% of adults. It is characterized by extreme itching, dry skin, scaling, erythematous papules, excoriations and exudates. These symptoms may be associated with frequent skin infections, as well as an increased incidence of allergic rhinitis, food allergy, and asthma.

The clinical course of eczema varies significantly among patients—from very mild itching and skin rash to severe cases
of skin infection requiring intensive treatment. While the condition is usually seen in early childhood, AD can present initially in adulthood. Typically, the rash has a symmetrical distribution, concentrating in the flexural folds of the arms, backs of the legs, and neck. Eczema is considered a result of a complex relationship between genetics, environment, immune system dysregulation and skin barrier dysfunction.

Atopic dermatitis symptoms often disrupt quality of life by affecting sleep and self-esteem, as well as school and work attendance. Although eczema is not a curable disease, it usually can be successfully managed by a combination of skin care, avoidance of triggers, infection control, stress management and medical treatment.

**Genetics Affecting Eczema**

Genetics greatly affect the risk of developing eczema. For example: in a set of twins, when one twin has AD, the likelihood of the second twin developing AD is several times greater than that of the general population. While this illustrates the genetic nature of AD, there is no simple inheritance pattern to explain the disease. Instead, AD is thought to be the result of multiple genetic polymorphisms. Loss-of-function mutations of the epidermal barrier protein filaggrin predispose a subset of patients to developing AD. Other gene loci may be impaired in AD. These genes control T helper cell cytokine genes such as IL-4, IL-5 and IL-13. These cytokines are overproduced in atopic individuals and are linked to the IgE response to allergens as well as eosinophilia. There is a high concordance rate of AD among both fraternal and identical twins, indicating a definite role of genetics in development of the disease.
Natural History of Eczema

Although worldwide prevalence of eczema varies, the occurrence in U.S. school children is roughly 17%. Atopic dermatitis can be mild (80% of cases), moderate (18% of cases), or severe (2% of cases). In about 80% of affected children, the disease presents prior to their fifth birthday. More than 60% of AD-affected children experience resolution by adolescence. Further, more than 60% of AD-affected children are at risk for developing either respiratory allergy or asthma. In those patients with more severe disease in childhood, it is more likely to persist into adulthood.

Eczema and Increased Incidence of Allergies

Eczema is related to the development of food allergies, allergic rhinitis, and asthma. In most patients with AD, there is an increased production of IgE in response to environmental allergens and food proteins. In fact, the total IgE level can be very high in active AD.

Role of the skin as a barrier

Does the rash cause the itching and scratching? Or does the itching and scratching cause the rash? It is unclear which comes first. It is known that the breakdown of the skin barrier by scratching and irritants can cause an AD flare. Further, the resulting pro-inflammatory cascade occurring within the skin can induce a patient to scratch more, further damaging the skin. This sequence evolves into an itch-scratch-itch cycle.

In normal skin, the stratum corneum of the epidermis is made up of desmosomes linking keratinocytes together. A lipid matrix made up of cholesterol, ceramides and fatty acids is
crucial in protecting the skin barrier as well. AD is associated with breakdown of this barrier, including reduced ceramide levels, increased transepidermal water loss and increased activity of endogenous proteolytic enzymes. This barrier can be further weakened by exogenous proteases (e.g. dust mite allergens or exotoxins from Staph aureus bacteria). Therefore, dust mites and staph aureus are two potential triggers of AD.

Clinical Features of Atopic Dermatitis

The diagnosis of atopic dermatitis is based on the presence of major and minor features.

Acute AD is characterized by intensely pruritic, erythematous papules associated with excoriations, vesiculations, and serous exudate. Subacute AD is characterized by erythematous, excoriated, scaling papules. Chronic AD is characterized by thickened skin (lichenification) with accentuated markings and changes in pigmentation and fibrotic papules. Patients with chronic AD may have all three types of lesions simultaneously. In addition, patients usually complain of dry skin.

During infancy, AD primarily affects the face, the scalp, and the extensor surfaces of the extremities. The diaper area is usually spared, but if involved, it may be secondarily infected with Candida, in which case the dermatitis does not spare the inguinal folds. In contrast, lower extremity involvement is a common distribution in children. In older patients with long-standing disease, the flexural folds of the extremities are the predominant location of lesions (popliteal fossa and antecubital fossa). Localized AD involving the eyelids and periocular skin more often affects adults and may be an isolated manifestation, but it should be differentiated from allergic contact dermatitis.
Ocular Complications of Atopic Dermatitis

Atopic keratoconjunctivitis is almost always bilateral, and symptoms include itching, burning, tearing, and mucoid discharge. It is frequently associated with eyelid dermatitis and chronic blepharitis and may result in visual impairment from corneal scarring. Keratoconus is a conical deformity of the cornea that is believed to result from persistent rubbing of the eyes in patients with atopic dermatitis and allergic rhinitis. Anterior subcapsular cataracts may develop during adolescence or early adult life as a complication of AD.

Hand Dermatitis Complicating Atopic Dermatitis

Patients with atopic dermatitis often have non-specific hand dermatitis. This is frequently irritant in nature and aggravated by repeated wetting or washing, especially in the occupational setting. A history of past or present AD at least doubles the effects of irritant exposure and doubles the risk in occupations where hand eczema is a common problem.

Skin Infections Complicating Atopic Dermatitis

Patients with atopic dermatitis have an increased susceptibility to infection or colonization with a variety of organisms. These include viral infections with herpes simplex, molluscum contagiosum, and human papillomavirus. A direct relationship has been demonstrated between interferon-γ (IFN-γ) concentrations and the cytopathic effect of herpes simplex. Also, an inverse relationship has been established between IL-4 and the cytopathic effect of herpes simplex, suggesting that the T cell-associated cytokine abnormalities...
seen in AD can enhance the effect of viral infections, like herpes.

A number of studies have noted the importance of Staphylococcus aureus in AD. The higher rate of S. aureus colonization in AD lesions compared to lesions from other skin disorders may also be associated with staph colonization of the nares, with the hands serving as the vector of transmission.

Patients without obvious superinfection may have a better response to combined antistaphylococcal and topical corticosteroid therapy than to corticosteroids alone. Although recurrent staphylococcal pustulosis can be a significant problem in AD, invasive S. aureus infections occur rarely and should raise the possibility of an immunodeficiency such as hyper-IgE syndrome. Chronic skin inflammatory lesions in AD reveal dry, thickened, lichenified (leather-like) skin that is often hyper or hypo-pigmented. AD usually follows a chronic relapsing course which may flare due to allergens, changes in temperature and/or humidity, and stress.

Psychological implications of Atopic Dermatitis

Patients with AD may have higher levels of anxiety and problems dealing with anger, hostility and frustration. Although these emotions do not cause AD, they can exacerbate the illness. Patients often respond to stress or frustration by itching and scratching. Stimulation of the central nervous system may intensify cutaneous vasomotor and sweat responses and contribute to the itch–scratch cycle. In some instances, scratching is associated with significant secondary gain or may be a strong component of habit. Severe disease can have a significant impact on patients, leading to problems with social interactions and self-esteem. Of considerable importance, sleep disturbance due to itching is common in this
chronic disease and significantly impacts on the quality of life of patients and family members.

**Treatment of Eczema (Atopic Dermatitis)**

The treatment of AD must be optimized for each patient, taking into consideration the role of environment, allergens, irritants, response to medication, and psychosocial stresses in the disease process. Patients and/or their families must also be counseled that AD is a chronic disease that cannot be cured but can usually be successfully managed with proper daily care.

**Eliminate exacerbating factors**

Patients with AD have a lower tolerance to environmental irritants, which include: detergents, soaps, chemicals, pollutants, abrasives, extreme temperatures and humidity. All cleansers and detergents should be fragrance- and irritant-free. Soaps with minimal defatting activity and neutral pH should be used (e.g., Dove, Neutrogena, Cetaphil).

Clothes should be rinsed twice in the wash, without fabric softener that may irritate the skin. All new clothing should be washed before wearing to remove chemicals. Some irritating fabrics such as wool should be avoided altogether. Air conditioning should be used in the summer. Hot, humid weather and sweating can flare AD. In the winter, judicious use of a humidifier can help with dry, itchy skin. Occlusive clothing should be avoided, and cotton or cotton blends are recommended. The temperature in the home and work environments should be temperate to minimize sweating. Cotton (100%) mitten sleeves are very helpful for **infants**, **children** and even **adults** to prevent the trauma of scratching the skin.

Other irritants may include chlorine or bromine in swimming
pools, although swimming and sun exposure themselves may be beneficial for AD patients.

**Allergens / irritants**

Allergy skin testing or RAST/Immunocap™ assay is valuable in the identification of environmental and food allergies contributing to AD. Specific IgE measurement using a lab assay can also assess sensitivity to certain foods such as eggs, milk, peanuts and fish. There is some proof that reducing dust mite exposure in dust-allergic patients may improve AD. This includes using dust mite encasements on mattresses and pillows, removing carpets and washing linens in very hot water.

Positive allergy skin tests are considered relevant when they correlate with the patient’s allergy history. This is an important point since some patients with AD produce large amounts of specific IgE that does not appear clinically relevant.

**Hydration / moisturizers**

Daily skin care and moisturizing is imperative when treating AD. Improving skin hydration helps to restore skin barrier function. Daily baths in warm water lasting 10-20 minutes followed by immediate application of an effective emollient cream or ointment to lock in moisture are recommended. Some patients may use oatmeal baths to soothe the skin. Moisturizers should be scent- and irritant-free. Ointments are generally preferred, as they tend to have fewer preservatives. Crisco shortening can even be used as an inexpensive moisturizer. Newer barrier creams have been developed that help repair the skin barrier (e.g., Atopiclair, Epicream, and Mymyx). These newer barrier creams can help restore the integrity of the dry skin in AD and offer great benefit to many patients. All of these newer barrier creams require a prescription.
Wet wrap dressings at bedtime can be used in cases of severe flares of AD by decreasing the itch and inflammation. The wet bandages are placed over a dilute corticosteroid preparation on the skin. The area is then over-wrapped with a dry bandage. This can be done for several nights. When the skin is inflamed and covered with pus, gently use wet dressings to remove pus and bacteria prior to applying therapy to the underlying inflamed skin (see antibiotic treatment below).

Everyday skin care for AD

A simple and basic regimen is key to effective AD management. Staying with one well-tolerated soap and one moisturizer is very important. Using multiple soaps, lotions, fragrances, and mixes of products may cause further irritation of sensitive skin.

Maintaining the skin barrier will prevent further damage and enhance the patient’s quality of life. An effective daily skin care routine is critical in preventing recurrent episodes of symptoms. Key factors are proper bathing and the application of lubricants, such as creams or ointments. People with atopic dermatitis should avoid hot or long baths and showers (more than 20 minutes). A warm bath helps to cleanse and moisturize the skin without drying it excessively. The doctor may recommend limited use of a mild soap or non-soap cleanser (Cetaphil) because soaps can be drying to the skin. Bath oils are not usually helpful.

Once the bath is finished (10-20 minutes), the patient should air-dry the skin or pat it dry gently with a soft towel (avoiding rubbing or brisk drying) and apply a lubricant immediately. Lubrication locks in the skin’s moisture acquired from bathing, increases the rate of healing, and establishes a barrier against further drying and irritation. Several kinds of lubricants can be used. Lotions are generally not the best choice because they have a high water or alcohol content and evaporate quickly. Creams and ointments work better in healing
the skin. Tar preparations can be very helpful in healing dry thickened, lichenified areas. The chosen preparation should be as free of fragrances and chemicals as possible.

Another key to protecting and restoring the skin is taking steps to avoid repeated skin infections. Although it may not be possible to avoid infections altogether, early identification and treatment is best.

**Corticosteroids**

Topical corticosteroids remain the first line of active treatment for AD and when employed judiciously, their efficacy far outweighs any potential side effects. Topical steroid creams and ointments reduce both inflammation and pruritus. Corticosteroids vary in their potency (see Table 3). The vehicle used in the preparation can also alter the penetration and efficacy of the steroid. Rarely should steroids be used under occlusion as this may cause irreversible atrophic changes to the underlying skin.

In general, the use of medium to low potency steroids should not cause side effects if used properly. Side effects may include thinning of the skin, telangiectasia, acne, stria, and hypo pigmentation. Particular care should be taken when treating areas such as the face, eye area and groin as these areas are more susceptible to adverse side effects. In rare cases, patients can develop contact allergy to the steroid creams or their preservatives.

Steroids can come in many forms including lotions, creams, ointments, oils, foams and even tapes. Ointments are more occlusive and have longer staying power, but they are often too greasy for daily use. Foams are good for the scalp and beard area but may contain alcohol, which is drying. It is important not to abruptly discontinue topical therapy with a high potency corticosteroid, as this may cause a flare of AD. One should institute step therapy in AD moving from high
potency to a low potency therapy to avoid flares of AD. In general, oral prednisone should be used sparingly to manage AD, as its taper may be associated with a dramatic flare of AD symptoms.

In contrast, under treating AD may cause sleep loss, decreased work or school productivity, skin wounds, infection, and possibly psychosocial pathology.

**Topical calcineurin inhibitors (TCIs)**

TCIs are nonsteroidal immunomodulating drugs that block the inflammatory cascade produced by T-cells in the skin. There are two TCIs available in the U.S.: tacrolimus 0.03% and 0.1% ointment (Protopic) and Pimecrolimus 1% cream (Elidel). They are indicated for treatment of moderate to severe AD in non-immunocompromised adults and children older than two years. TCIs may cause transient burning when first applied. Since they do not cause skin atrophy, they can be used in the groin and on the face. TCIs have demonstrated low systemic absorption as compared to corticosteroids. Despite their inherent safety, TCIs carry a black box warning stating that “long-term safety has not been established.” As an immunosuppressive drug, there is a theoretical increased risk of malignancy.

**Tar preparations**

Although not as commonly used, crude coal tar extracts have mild anti-inflammatory properties that may help limit the use of corticosteroids. They are especially helpful on the scalp in shampoo form. The side effects are minimal and generally are limited to skin irritation, strong odor, photosensitivity and pustular folliculitis.

**Antibiotics**

It is not uncommon for secondary infection to occur in AD,
and it is often due to Staphylococcus aureus. Most patients with AD have higher levels of colonization with S. aureus. S. aureus secretes an exotoxin that causes local skin destruction and intense itching. In flares of AD when pustules are seen, short courses of either a semi-synthetic penicillin or a first- or second-generation cephalosporin for 7-10 days is usually effective. Chlorine or dilute bleach baths may also be helpful.

**Antipruritic agents**

Itching is the hallmark of AD and causes the most suffering in patients. In fact, from a diagnostic point of view, a rash without itching rules out atopic dermatitis as a diagnostic consideration. Typical antipruritic drugs such as antihistamines may not be completely effective in controlling AD itching because it is likely caused by cytokines or neuropeptides rather than histamine release alone. Most of the benefits of using antihistamines in AD patients may stem from their sedating and tranquilizing effects. Diphenhydramine, because of its quick onset and short half-life may benefit children while tricylic antidepressants such as doxepin may be helpful in treating adults. Use of topical antihistamines or topical anesthetics has been shown to cause sensitization in some patients and should be avoided.

**Allergen Immunotherapy**

Allergen immunotherapy has shown some promising initial results in the treatment of AD. The most convincing benefits in these studies were found in house dust mite-sensitized AD patients. The potential side effects of allergen immunotherapy (including anaphylaxis and worsening of AD) need to be considered. Further studies are needed to compare this therapy with conventional AD treatment before it is considered a viable option.
**Patient Education**

AD can be an extremely disruptive chronic condition that interferes with sleep, work and school. Relaxation techniques, biofeedback, massage therapy and even psychotherapy may be helpful. The patient must be educated regarding triggers of AD, as well as the chronic nature of this condition.

**Pruritus and sleep**

Severe itching can seriously interfere with sleep. Use of first-generation antihistamines (diphenhydramine, and hydroxyzine) at bedtime may be a good idea since they often have a sedative effect. Doxepin, benzodiazepines, and clonidine have been used at bedtime in AD-affected adults as sleep aids, although they are not specifically approved for this purpose.

**Food allergy and Eczema**

Nearly half of the children with moderate to severe AD suffer from some form of food allergy. The onset of reactions to foods may be immediate or delayed and may be associated with hives, itching and flares of AD, GI symptoms, or respiratory symptoms. Milk, soy, eggs, wheat, peanuts, shellfish, and tree nuts are the allergens that produce 90% of food allergy reactions.

Negative allergy skin testing for foods is 95% accurate. However, false positive tests are not uncommon and require a carefully monitored challenge to confirm the actual presence of food allergy. A history of food allergy triggering AD may be misleading. It should be supported by elimination of the suspected food and subsequent improvement of AD symptoms.
Skin infections and Eczema

It is common for secondary skin infections to occur in AD. These infections are often due to S. aureus. Most patients with AD have high levels of colonization. S. aureus secretes an exotoxin that causes local skin destruction and intense itching. In flares of AD when pustules are seen, short courses of either semi-synthetic penicillins or first or second-generation cephalosporins for 7-10 days are usually effective. For local areas of infection topical muropiricin (Bactroban) applied three times a day may also be effective. Treating nasal colonization of staph with nasal muropiricin twice a day for 5 days also may reduce flares of AD.

Although use of an antibacterial soap may decrease staph colonization of the skin, these soaps are often too drying and irritating. Instead, a mild lotion soap is preferred.

Another option is using bleach baths to decrease the incidence of skin infections. In this case, 1/8 cup of sodium hypochlorite (bleach) per full tub of water for a 10-15 minute soak several times a week may significantly reduce bacterial load and reduce flares in patients with persistent skin colonization.

In infants with extensive secondary skin infections or patients with persistent fevers, further work-up for more invasive infections (e.g., bacteremia, endocarditis, arthritis, osteomyelitis, bursitis) should be considered. Hospital admission for intravenous antibiotics and intensive nursing may be necessary.

Herpes simplex virus (HSV) can cause life-threatening eczema herpeticum in AD patients because of distinct susceptibility to this type of viral infection. Patients with eczema herpeticum may present with fever, malaise, and widespread vesicles. However, some HSV-superinfected AD lesions may not appear vesicular, but rather as punched-out lesions with an
erythematous base. HSV DNA polymerase chain reaction (PCR), Tzanck smear, or viral culture should be obtained from the lesion while the patient is started on intravenous acyclovir or other antiviral medication. Patients with periocular or ocular involvement should be evaluated by an ophthalmologist as an emergency. Since smallpox vaccine is no longer available, the resulting life threatening infection of eczema vaccinatum is no longer encountered.

Stubborn Atopic Dermatitis

Hospitalization

In rare cases of severe atopic dermatitis that are resistant to therapy or in patients with disseminated infection, short-term hospital stays may be necessary. Merely removing the patient from his/her environment and ensuring compliance with intensive skin care may result in marked clinical improvement.

Systemic corticosteroids

This is an aggressive treatment for symptomatic relief of a severe AD flare. A short 1-week course of systemic corticosteroids should be followed by a taper over a few days and more intensive daily skin care (i.e., increase bathing frequency and the amount and type of topical corticosteroids), due to the potential of rebound AD symptoms when discontinuing systemic corticosteroids. The side effects of repeat or prolonged courses of systemic corticosteroids include adrenal suppression, growth retardation in children, osteoporosis, hypertension, peptic ulcer, glaucoma, cataracts, and infections due to immunosuppression.
Cyclosporin A

In severe AD, intermittent or continuous treatment with low-dose cyclosporin A (2.5-5 mg/kg/day) for up to one year showed significant improvements in disease activity as well as decreases in pruritus and sleep disturbances in clinical studies. Use of cyclosporin is limited due to possible nephrotoxicity and is reserved for severe AD cases.

Phototherapy . PUVA

UV light therapy can be a very effective modality for treating stubborn AD, especially in those patients who are not light skinned and do not flare after sun exposure. Phototherapy exerts its effect by decreasing the expression of activated T-cells. UVA therapy has been used under medical supervision. This therapy may decrease dermal IgE binding cells and down regulate pro-inflammatory cytokines. Similarly, photochemotherapy using oral methoxypsoralen therapy followed by UVA (PUVA) is indicated for severe cases. Short- and long-term side effects may include pruritus, erythema, pigmentation, premature aging, and cutaneous malignancies. Natural phototherapy may also benefit patients, and sun exposure at the Dead Sea has been touted as a natural treatment for skin diseases including AD.

Azathioprine

Azathioprine has been shown to be effective in managing several dermatologic diseases and can be used in severe AD not responsive to other therapies. It acts as a systemic immunosuppressive agent and has the risk of numerous side effects including myelosuppression, hepatotoxicity, GI disturbance and increased risk of infection. Patients must be screened prior to treatment for levels of the enzyme thiopurine methyl transferase (TPMT) and the dose adjusted based on this level. Treatment may take months before an
Other treatments

There are several other therapies that have been used to treat severe AD, however, their benefit has not been proven. Probiotics have not been proven to be effective for AD, nor has the efficacy of Chinese medicinal herbs. There is currently no convincing data to support the use of intravenous immunoglobulin (IVIG) or Omalizumab (Xolair) to treat AD. Double-blind, placebo-controlled trials have failed to show the efficacy of montelukast.

Atopic Dermatitis: Conclusions

Atopic dermatitis is a common skin condition whose prevalence is on the rise among children and adults. As research continues to elucidate the many factors contributing to atopic dermatitis, we are better able to treat and manage the outcome. Crucial to management is identification of allergic triggers, daily skin care and intense patient education. Along with the excellent treatment options we have currently at our disposal, new insights into the origins and mechanisms behind AD should yield even better therapeutic alternatives in the future.

Hives

Hives (or urticaria) are itchy, red, often elevated skin lesions that whiten with pressure. Urticaria usually result from the release of mast-cell mediators (e.g. histamine, etc.) within the upper layers of the skin, causing blood vessel dilation, inflammation and local extravasation (or leakage) of fluid from capillaries into the skin. Hives come in all sizes and shapes, from tiny 2-3 mm to large irregularly shaped hives covering most of the body.
Other red, itchy rashes are often erroneously attributed to a diagnosis of hives. Individual inflammatory skin lesions persisting for days and resulting in lasting discoloration or hyper-pigmentation of the skin are probably not hives, but a result of some other inflammatory disorder (e.g. vasculitis). Skin biopsy of such lesions may be helpful in reaching the correct diagnosis.

Fortunately, even if an underlying cause cannot be identified, the majority of patients with hives can be successfully managed with a combination of medications and other preventive measures. Acute hives (detailed in the next section) are self-limited and resolve in days or weeks. In contrast, chronic hives recur over weeks, months and even years, but they can usually be controlled with continuous use of medication or an Injectable medicine called Xolair (omalizumab) which is given monthly. They often resolve following many months or years of treatment.

Angioedema often results from a similar release of mediators, involving the skin’s deeper cutaneous and sub-cutaneous tissues. In this case, more edema (fluid accumulation and swelling) is present than that seen with hives. Angioedema tends to be associated with marked swelling of the lips, tongue, peri-ocular tissues, and/or extremities. Angioedema of the GI tract can cause severe abdominal pain, while angioedema of the larynx or tongue can lead to respiratory distress.

**Urticaria: Acute vs. Chronic**

Hives that occur over limited periods of time, lasting hours, days, or occasionally, a few weeks are known as acute urticaria. By definition, acute urticaria persist for six weeks or less, whereas chronic urticaria persist for greater than six weeks. The cause of acute urticaria is often obvious because of the rapid onset of hives following exposure to a specific trigger.
Triggering events include exposure to a food, a medication, or an insect sting. Acute urticaria occur in more than 20% of the population at one time or another. In contrast, chronic urticaria occur in less than 1% of the population. Chronic hives may result from physical stimulation (e.g. heat, cold, rubbing of the skin, etc.), autoimmune disease, infections, or other underlying conditions. However, the condition may be classified as idiopathic when no identifiable cause can be determined.

Acute urticaria is a self-limited disorder that usually has an identifiable cause. An accurate patient history usually leads to the diagnosis.

Chronic urticaria may not have a clear etiology based on obvious historical evidence. In either case, a thorough history and comprehensive laboratory studies offer the patient the best chance of defining the cause of the hives.

**Causes of Hives: an In-Depth Look**

**Medications** can cause hives soon after exposure or several weeks following the introduction of a new drug. Drugs commonly associated with urticaria include penicillin and their derivatives, sulfonamides, analgesics (aspirin, Nonsteroidal Anti-inflammatory Drugs [NSAIDs]), radiocontrast media, sedatives, tranquilizers and diuretics. Drug-induced urticaria are often identified by elimination of the offending drugs with resolution of symptoms within days.

However, in some cases, symptoms may take months to subside. All medications taken by the patient including aspirin, NSAIDs, herbs and vitamins, over-the-counter medicines, topical creams, ointments, eye/nose/ear drops, birth control meds, suppositories and any injections should be discontinued if it is medically safe to do so when a drug-induced allergic reaction is suspected. If it is medically necessary to continue a suspect medication, consideration should be given
to replacing the medication with a suitable alternative of an unrelated drug class.

Angiotensin-Converting-Enzyme inhibitors (ACE inhibitors) trigger angioedema in a unique way. Although drug-induced angioedema is often temporally linked to the drug triggering the reaction, ACE inhibitors are the exception to the rule. Angioedema resulting from ACE inhibitors can occur months or years following the initiation of treatment and may only occur sporadically, thus obscuring the relationship between cause and effect. Angiotensin II Receptor Blockers (ARBs) have also been implicated in this phenomenon.

Unfortunately, there are no reliable allergy skin tests or laboratory tests specifically designed for identifying drug allergies except for penicillin.

**Non-immunologic induction of hives** occurs by direct mast-cell degranulation and does not appear to be IgE-mediated. Medications such as Vancomycin or narcotics (morphine, Demerol, codeine) can cause hives by directly stimulating the mast cell to release histamine and other mediators.

**Food-induced hives** are often obvious, as they evolve shortly after eating the suspected food. Diagnostic studies including allergy skin testing, lab testing (Immunocap™), elimination of the suspected food, or the double-blind food challenge (the gold standard) may be necessary to confirm the diagnosis.

Less commonly, a food eaten on a regular basis may contribute to chronic hives in a more subtle manner. These foods may contain food additives, often in minute amounts. Such additives include: food coloring agents, preservatives (antioxidants, anti-browning agents), emulsifying agents, stabilizers, gums, acidulants, enzymes and leavening agents. Specific agents implicated in allergic reactions include: monosodium glutamate, aspartame, parabens, BHA/BHT, sulfites, Tartrazine/FD&C dyes, and nitrates/nitrites. Consequently,
food challenges are often the only means of identifying the role of these hidden additives.

Moreover, the offending allergen may not be the food, food additive or preservative at all, but a contaminant in the preparation process or a high level of histamine-like substances in the food (pseudo allergen). In any case, a careful food history in combination with diagnostic testing or challenge performed by an allergy specialist can often isolate the triggering food product.

Auto-immune disease and other underlying medical disorders can cause hives and angioedema. Examples include systemic lupus erythematosus, cancer, vasculitis, Sjogren’s Syndrome, rheumatoid arthritis, and cryoglobulinemia. A skin biopsy of a persistent hive can help diagnose underlying vasculitis by revealing the presence of necrosis of blood vessels, leukocyte infiltration, and deposition of immunoglobulins and complement. A biopsy may also lead to diagnosis of an unsuspected disease such as cancer.

Infections can cause chronic urticaria, although this is uncommon. Examples include viral infections such as infectious hepatitis and mononucleosis—both of which are self-limited and fungal infections including thrush, tinea pedis, and tinea capitis. Many helminthic infections (roundworms) can cause chronic urticaria and include infestation of: ascaris, ancylostoma, strongyloides, filariae, echinococcus, schistosoma, trichinella and toxocara. These infections are usually associated with significant eosinophilia and elevated levels of IgE. Stool evaluations for ova and parasites can confirm the diagnosis. A good travel history can be helpful in this diagnosis.

Physical Urticaria and Angioedema

Hives and swelling triggered by a physical stimulus to the skin are known as physical urticaria. It is thought that
physical stimulation (light, heat, cold, pressure) leads to a change in local IgE that then stimulates mast cells to liberate mediators that cause the itching and hives.

**Local heat urticaria**

Local heat urticaria is triggered by skin contact with a warm stimulus. The diagnosis can be confirmed by applying a test tube of warm water (44 degrees Fahrenheit) to the arm for 4-5 minutes to check for the evolution of hives.

**Cholinergic or systemic heat urticaria**

Cholinergic urticaria consists of tiny wheals (2-3 mm) surrounded by a large border of erythema. Triggers include exercise, anxiety, sweating and hot showers. Typically, hives begin over the upper body and spread across the skin surface. An intradermal injection of methacholine reproduces these tiny hives and is diagnostic of this disorder. Running or bicycling for 15 minutes in an 85-degree room may be the best test.

**Pressure urticaria**

Pressure urticaria is characterized by a delayed swelling that occurs 4-6 hours after pressure has been applied. There is a great deal of local swelling, but no wheal and flare at the site. However, a biopsy may be helpful in the diagnosis of pressure urticaria.

A sling placed over the forearm or shoulder with a 10- or 20-pound weight for 10-20 minutes is an accurate test for this condition. The delayed swelling may present as burning or pain rather than itching. Pressure urticaria often affects the soles of the feet after standing for long periods of time, especially on hard, irregular surfaces. Treatment consists of low-dose corticosteroids (15-25 mg of prednisone every other day), since antihistamines and other common urticaria medications have proven ineffective.
Dermatographism

Also known as “skin writing,” dermatographism occurs when the skin is stroked, provoking a hive along the area of trauma. Using a tongue depressor to “write” on a patient with dermatographism will quickly produce a wheal and flare reaction that will last for 15-20 minutes or longer and confirm the diagnosis. This condition is very common and may occur in up to 5% of the population. Hives occur often occur along common areas of physical pressure (waist, sock line, bra line, etc.). Treatment consists of various combinations of antihistamines.

Solar or actinic urticaria

Hives and pruritus develop following brief exposure to light is known as solar urticaria. Hives result from exposure to certain wavelengths of light and typically are limited to sun-exposed areas. Symptoms often resolve quickly. However, in rare instances, generalized light exposure can lead to anaphylaxis. There are different types of solar urticaria, which are classified according to the wavelength of light that induces the eruption. A diagnosis is made by testing patients with specific wavelengths of light. Effective therapy varies depending on the type of solar urticaria. Sunblock containing zinc oxide, titanium oxide, or both are particularly effective in avoidance treatment.

Aquagenic urticaria involves an outbreak of hives following contact with water that is not temperature-dependent. The diagnosis is confirmed by placing a compress with distilled or tap water against the skin for a few minutes (the water should be tepid). Other forms of physical urticaria must be ruled out before making the diagnosis.

Cold urticaria is characterized by the rapid onset of pruritus, erythema and swelling following exposure to a cold stimulus. The swelling is local to the site of exposure.
Initially, symptoms get worse as the skin is warmed. Swimming in cold water can lead to anaphylaxis and drowning. Therefore, individuals with cold urticaria should always swim with a buddy, and an Epi-pen™ should be kept readily available. Many cases of cold urticaria are IgE-mediated, but cold urticaria may be associated with other diseases including: cryoglobulinemia, cold agglutinin disease, cryofibrinogenemia, and paroxysmal cold hemoglobinuria. The treatment of choice is with the antihistamine cyproheptadine (Periactin) for cold urticaria.

Exercise-induced hives may be a variant of vibratory or heat-induced hives. Usually symptoms evolve in conjunction with prolonged walks or exercising. Symptoms may be limited to intense itching or may evolve into generalized hives, which ultimately subside following cessation of exercise. It is often best treated by taking an antihistamine 1-2 hours before exercising. A severe form of this phenomenon is that of exercise-induced anaphylaxis in which the patient becomes hypotensive and breaks out in hives. This latter form of exercise-induced hives is preventable in some patients by avoiding meals for 4 hours prior to exercise, which indicates that it may be a food-dependent reaction. Pre-treatment with an antihistamine is recommended, along with making sure an Epi-pen™ is on hand.

Cutaneous vasculitis

Biopsy of hives which last more than 24 hours may reveal a necrotizing vasculitis involving small vessel infiltrates. Individual hives resolving within 24 hours without inflammation are rarely a sign of vasculitis. Immunofluorescent studies reveal the presence of immunoglobulins and complement. Systemic vasculitis with hives often has elevated sedimentation rates, arthralgia, fever, etc. Cutaneous vasculitis is often associated with low complement levels (hypocomplementemic vasculitis), in which
the vasculitis is limited to the skin without other systemic involvement.

**Papular urticaria**

Multiple insect bites can lead to a pruritic, local papular rash known as papular urticaria. This condition is often observed on the skin of the lower extremities and may be due to bed bugs, mosquitoes, fleas, chiggers, and other insects that attack the exposed skin. Lesions are red, and unlike hives, they do not blanch. They often last days or weeks.

**Urticaria pigmentosa**

Urticaria pigmentosa is a form of cutaneous mastocytosis. The rash consists of slightly elevated brownish macular lesions resulting from concentrations of mast cells on the surface of the skin. When these macules are stroked, mast cells release mediators which trigger the local appearance of hives. Urticaria pigmentosa may consist of a few isolated lesions or dozens of macules over large areas of the body. In children, lesions are usually larger and well demarcated. In adults, they may be numerous, slightly elevated, reddish-brown papules. When lesions cover most of the skin surface, it is referred to as diffuse cutaneous mastocytosis. Usually the face, scalp, palms and soles are spared.

**Chronic idiopathic urticaria and idiopathic angioedema**

For many physicians and patients, the management of chronic urticaria is frustrating because of the lack of an identifiable cause, and the variable response to medical therapy. Less than 25% of individuals with chronic urticaria
have an identifiable cause of their rash. The remaining 75% are referred to as chronic idiopathic urticaria or hives “without a known cause.” If only a small number of chronic urticaria sufferers have an identifiable cause, why work up patients so thoroughly?

There are two reasons:

1. In the event that a cause can be identified, the trigger can either be eliminated or managed more effectively with a focused, therapeutic approach.

2. It is medically necessary to rule out an underlying medical condition.

Patients with chronic idiopathic urticaria usually have normal blood work and no signs of underlying systemic disease. Some studies have shown that up to 40% of such patients appear to have an autoimmune cutaneous disorder. Skin biopsy reveals a non–necrotizing perivascular, mononuclear cell infiltrate. Frequently, an increase in mast cells and basophils is also noted. Further, the skin biopsy reveals an increase of CD4+ cells, neutrophils, and eosinophils, similar to that seen in late-phase allergic reactions.

In the New England Journal of Medicine, Hide, Francis and Grattan, et al. reported the presence of anti-IgE receptor antibodies in 30-40% of patients with idiopathic urticaria. These patients suffer from an autoimmune disease in which auto-antibodies are directed at the IgE receptors on mast cells causing release of mediators which induce hives.

**Hereditary forms of urticaria and angioedema**
**Familial cold urticaria**

This is a form of periodic fever, a rare form of cold intolerance inherited as an autosomal dominant trait. Cold exposure causes a burning rash, fever, chills, arthralgia, myalgia, headache, and leukocytosis.

Familial cold autoinflammatory syndrome is characterized by frequent hives with cold exposure and may be treated with either anakiruen (Kinerat) or canukinumub (Ibolis).

**Hereditary vibratory angioedema**

This reaction consists of pruritus and swelling minutes after a vibratory stimulus. Treatment consists of avoidance of vibratory stimulation and use of antihistamines.

**Hereditary angioedema (HAE) and acquired C1-INH deficiency**

Hereditary angioedema is due to an autosomal dominant disorder resulting in a decrease in the quantity and/or function of C1-esterase inhibitor concentrate (C1-INH). It affects any part of the body, including the tongue, larynx, extremities and intestines.

Hives and itching are always absent. Episodes often last days. GI symptoms often mimic an acute abdomen or abdominal obstruction. Biopsy shows no cellular infiltrate and the edema results from the release of vasoactive factors such as kinins.

Low or absent C1-INH levels lead to complement consumption with decreases in C3 and C4. In fact, patients often have a low C4 level even if symptoms are not active. A decreased quantitative C1-INH level is diagnostic, however 15% of these patients may have normal quantitative C1-INH levels that are defective, requiring a functional assay for C1-INH to confirm the diagnosis.
Treatment of hereditary angioedema is unique. It doesn’t respond to epinephrine, steroids, antihistamines or leukotriene antagonists, usually effective in treating allergic angioedema. Instead, the stimulation of the hepatic production of C1-INH by the use of anabolic steroids such as Stanazole has been used to prevent attacks in the past.

Less commonly, fresh frozen plasma concentrate infusions are used to treat acute symptoms. The good news is that C1-INH concentrate infusions that have been available in Europe for decades and are now approved for use in the United States. An infusion of C1-INH concentrate will quickly resolve active symptoms of HAE by restoring the proper balance of inhibition of this system. Other drugs used to treat angioedema as seen in HAE include brodykin medicated Firuzeyr or escallantide.

When upper airway angioedema does not respond to medical treatment, a tracheotomy is the procedure of choice to restore a patient’s airway. Finally, low C1-INH levels and resulting angioedema may be the result of an underlying autoimmune disease or cancer in which the underlying disease inactivates C1-INH and effectively creates the same clinical symptoms as seen in hereditary angioedema.

Angioedema in-depth

Angioedema, or deep swelling of the soft tissue, may be a result of drug allergy, food allergy, bee sting allergy, complement disorders, or autoimmune disease as well as other uncommon or rare disease processes. In contrast to urticaria, angioedema is often not pruritic (itchy), but rather, can be painful and tender. Allergic triggers of angioedema are typically IgE-mediated and are often easily identified based on the demonstrated temporal relationship between exposure and development of symptoms.

A family history of angioedema might point to a unique disorder known as CI-INH deficiency, or hereditary angioedema
In this disorder, there is a deficiency in the quantity and/or function of the enzyme C1-INH. This deficiency results in episodes of angioedema which can involve the skin, the airway, and/or the GI tract. Episodes of angioedema related to this disorder can be severe and life-threatening and respond poorly to conventional therapy. Unique to this form of angioedema is the absence of urticaria or itching.

**Laboratory work-up for chronic idiopathic urticaria (no cause) and angioedema**

- CBC with differential
- Erythrocyte sedimentation rate (ESR)
- Anti-nuclear antibody (ANA)
- Urinalysis Liver function tests (LFT)
- Tests for mononucleosis and hepatitis
- ANCA (for patients with vasculitis)
- Thyroid profile and thyroid autoantibodies
- Complement profile (C3, C4, CH 50) C1 INH levels (quantitative and functional) for angioedema
- Tryptase level
- Cryoglobulins (for cold-induced urticaria)
- Stool for ova and parasites
- Skin biopsy, immunofluorescence

**Managing chronic urticaria**

1. **H1 antihistamines.** Histamine released from mast cells is the primary chemical mediator involved in the development of urticaria. Antihistamines competitively bind histamine receptor sites in the skin, thus suppressing the development of hives and the related pruritus (itching).

   Non-sedating antihistamines such as loratadine (Claritin),
desloratidine (Clarinex) and fexofenodine (Allegra) are best administered in the morning, in order to avoid drowsiness and impairment of function as seen with first-generation antihistamines. Zyrtec (Cetirazine) and Xyzal (Levocetirizine) are minimally sedating and appear to be well-tolerated by most patients.

Some patients are fortunate and their urticaria can be controlled with a single, daily dose of the non-sedating or minimally sedating antihistamines, however, many patients with chronic urticaria require multiple antihistamines, often at higher than conventional doses. The non-sedating/minimally sedating newer H1 antihistamines are frequently administered in combination with older generation H1 antihistamines such as Benadryl (diphenhydramine) and Atarax (hydroxyzine), which are often administered at night.

Doses of hydroxyzine or diphenhydramine between 25 and 50 mg up to four times per day may be required in order to provide adequate control of symptoms. Physicians and patients must be mindful of the possible sedating and anticholinergic side effects of these older agents and take the necessary precautions.

2. **H2 antihistamines** (e.g. ranitidine, cimetidine) benefit a number of patients with hives when taken in conjunction with H1 antihistamines, resulting in better overall control.

3. **Leukotriene receptor antagonists** such as Singulair (montelukast) have proven effective in some patients with chronic urticaria and angioedema, apparently by blocking the leukotriene pathway, which plays a role in mast cell-induced inflammation.

4. **Oral corticosteroids**. (e.g. prednisone, methylprednisolone, Medrol) are powerful anti-inflammatory medications which are highly effective in the management of urticaria. Most patients will experience significant relief of their hives with an
oral corticosteroid. Initially, a tapering course of prednisone (30-40 mg/day) will prove effective in controlling severe cases, but as the dose is tapered, hives may have a tendency to recur. Some patients will require low-dose daily treatment (5-10 mg daily) while others can benefit from alternate-day treatment in which a low dose is given every other morning. Alternate-day treatment with corticosteroids allows control of hives without the potential for steroid dependency associated with long-term use of daily steroids. Extreme caution must be exercised with the administration of short courses or chronic use of oral corticosteroids.

5. **Xolair**—a novel biologic injection that was initially approved for moderate to severe asthma is also approved for treatment of chronic hives. Response rates with Xolair range from 70%-80% and has been very effective in reducing or eliminating refractory hives. Special testing may be required before initiating Xolair treatment.

### Managing angioedema

Allergic (histamine driven) angioedema resulting from mast cell mediator release and inflammation often responds well to corticosteroids. However it may take hours or days to respond to this therapy. In emergency management of angioedema (e.g. airway obstruction), an injection of epinephrine (.3-.5 cc) is often effective within minutes and can be life saving. HAE and acquired C1-INH deficiency-related angioedema is often difficult to treat with poor a response to epinephrine and other corticosteroids. Effective treatment involves administration of medication which promote C1 INH production and/or administration of C1 INH.

An infusion of C1-INH concentrate or bradykinin inhibitors will quickly resolve active symptoms of HAE or nonallergic (bradykinin driven angioedema) by countering the effect of
bradykinin in the system. When upper airway angioedema of any type does not respond to treatment and the airway is significantly obstructed, then a tracheotomy is the procedure of choice.

In summary, chronic urticaria and angioedema are varied in their mechanisms and presentations and will often require comprehensive investigations in order to identify a cause. Fortunately, even those with chronic conditions without a clear cause often respond to carefully planned maintenance programs and emergency backup, which will ultimately lead to a better quality of life.