Water Allergy and other Tales from the Bizarre World of Urticaria

Aquagenic Urticaria

Contact Sensitivity Reaction to Water

WATER is the most trusted compound in the universe. As the very essence of life, it is considered safe above all else. We bathe in it, we drink it, we live by it, asking of it only purity. Hence, it is with difficulty that one comes to realize that some individuals react adversely to simple contact with water.

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Introduction

Urticaria is a relatively common condition that affects a sizeable fraction of the population. Despite its common occurrence, it often is misdiagnosed and certainly misunderstood, even by specialists. While there are enumerable etiologies for urticaria as a symptom, I would like to focus this Grand Rounds on chronic urticarial diseases. This group of disorders presents with similar lesions, but the etiologies are significantly different and the cause for most patients with chronic urticaria is unknown. Finally, while allergy is a common cause of brief urticarial symptoms, it is rarely if ever a cause of chronic urticaria, a common misconception.

History of "Urticaria"

Hippocrates described elevated itchy lesions caused by nettles and mosquitoes. He called these lesions "knidosis" after the Greek word for nettle (knido).[1] Jean-Louis Alibert used the same term in his book on skin diseases published in 1833. Plinius introduced the term "uredo" meaning burning and this term was used for centuries by European and Arabic physicians. Zedler in his "Grosses vollständige Universallexikon" changed uredo to the term "urticatio". The word urticaria was first introduced in 1769 by William Cullen in his book "Synopsia Nosalogiae Methodica".[2] Thomas Bateman published an influential work "A Practical Synopsis of Cutaneous Diseases" in 1813 which was the completion of the work by his colleague Robert Wilan.[3] In this book, several types of urticaria were described including "urticaria evinada" where new lesions can continue to appear for many months or years, what we now call chronic urticaria. Many of the physical urticarias were described as early as the 18th century including factitious urticaria or dermographism. This condition may have represented one of the "witches' mark" which led to burning or being beheaded in the Middle Ages.

Classification

Urticaria has been arbitrarily classified primarily based on the duration of the urticarial episodes. Typically, urticarial episodes that last <6 weeks are considered acute urticaria. Common causes of acute urticaria include IgE-mediated etiologies such as food allergy, drug allergy, and stinging insect reactions. In children viral infections are a common cause of acute urticaria. Nonetheless, in many patients with acute urticaria, an etiology may not be found. Chronic urticaria (CU) has been defined as having urticarial episodes that last > 6 weeks. Most patients have urticarial lesions daily or several days per week. Although a number of etiologies have been attributed to cause CU, the three most common etiologies are idiopathic, autoimmune, and physical urticarias. Some patients with recurrent urticarial episodes do not appear to fit exactly into the acute or chronic classification scheme. These patients may have episodes of urticaria that last < 6 weeks but recur frequently. Whether these patients have recurrent acute urticaria or chronic intermittent urticaria is unclear, but my personal approach is to evaluate and manage them analogous to CU patients.

It should be noted that angioedema (tissue swelling) is a common symptom in patients with urticaria, occurring in approximately 50% of cases. The presence of angioedema does not aid in classification, diagnosis, or treatment. However, angioedema in the absence of urticaria involves a separate differential diagnosis including bradykinin-mediated angioedema conditions such as C1-esterase inhibitor deficiency syndromes (e.g. hereditary angioedema) or ACE-inhibitor angioedema.

Epidemiology

The epidemiology of urticaria has not been adequately studied and data are especially lacking for the United States. Approximately 20% of the population may have acute urticaria at some point in their lives. This statistic has not changed much from a study conducted in 1969 in England[4] to a more recent telephone survey in Spain from 2004.[5] The prevalence of CU in the general population has not been adequately studied. In the aforementioned Spanish telephone survey, 0.6% of respondents gave a history consistent with CU. One German study found that ~3% of both a general practitioner's patients as well as a dermatologist's patients had some form of urticaria.[6] Anecdotally, many allergists in the U.S. feel there has been an increase the number of patients they are seeing with CU, but whether this is indeed fact or perception remains to be proven.

Pathophysiology

While several mediators may be responsible for urticarial lesions, histamine appears to be the most prominent mediator in most cases. Histamine is an inflammatory mediator that induces the classic triple response of vasodilation (erythema), increased vascular permeability (edema) and an axon reflex that increases the extent of the reaction. This axon reflex appears to be due to release of substance P from nonadrenergic, noncholinergic type C fibers by antidromic conduction. When injected into the skin, histamine causes an urticarial lesion. A comparison of tissue histamine concentration from 13 patients with urticaria, found 12/13 with elevated tissue histamine from lesional skin as compared to non-lesional skin.[7] A number of other mediators have been shown to have a role in urticaria as shown in Table 1.

Table 1. Mediators of Urticaria and Angioedema

Mast cells/basophils	Histamine, PGD_2, cys-leukotrienes, PAF
Complement system	Anaphylatoxins (C3a, C5a)
Coagulation Pathway	Bradykinin, thrombin
Neuropeptides	VIP, substance P

Acute Urticaria

Acute urticaria is often a symptom of many other allergic diseases involving IgE sensitization such as food allergy, insect allergy, or drug allergy. In patients with IgE-mediated urticarial reactions, the potential for multi-organ anaphylaxis exists and the use of epinephrine as well as a prescription for self-injectable epinephrine should be considered. Numerous other non-IgE dependent etiologies may cause acute urticaria including infections, serum sickness, complement mediated reactions, mast cell activating substances (e.g. vancomycin, opiates), and toxins (e.g. scombroid). However, many cases of acute urticaria have an unknown etiology and are termed idiopathic. Medications may also cause recurrent acute urticaria/angioedema. Aspirin and

NSAIDs are common causes of recurrent acute urticaria and reactions to these agents is associated with an increased risk for the subsequent development of CU.[8] ACE-inhibitors may be associated with recurrent angioedema. A recent retrospective study found a mean of 1.8 years from initiation of ACE-inhibitor until the onset of angioedema.[9] Characteristically, ACE-I angioedema involves the head and neck primarily, especially the lips and tongue, but rarely presents with concomitant urticaria.

A thorough history is appropriate in acute urticaria as well as appropriate diagnostic testing in the cases of IgE-mediated food and insect reactions. In the absence of a historical trigger, no diagnostic evaluation is required for cases of acute urticaria. Unfortunately, there are no clinical features that will predict which patient that presents acutely with urticaria/angioedema will persist into CU.

In regards to management of acute urticaria, antihistamines and glucocorticoids are the mainstays of treatment. Few studies have evaluated the effects of systemic corticosteroids on acute urticaria. A randomized open-label study of loratadine or prednisolone in 109 patients with acute urticaria showed both treatments to be effective with a higher frequency of remission within 3 days with corticosteroid therapy.[10] A double-blind study of 43 acute urticaria patients evaluated treatment with diphenhydramine intramuscularly followed by hydroxyzine plus prednisone or placebo for 4 days.[11] The prednisone treated group had greater clinical improvement at both 2 and 5 days of follow-up.

Several studies have evaluated the role of H2 antagonists either alone or in combination with H1 antagonists. A double-blind study of 93 acute urticaria patients presenting to an emergency department compared intramuscular diphenhydramine with intramuscular cimetidine.[12] Both treatment groups had high rates of patient reported improvement 30 minutes after the injection, however no placebo arm was included in the study. Another smaller study showed similar results with similar efficacy between intramuscular famotidine alone and intramuscular diphenhydramine.[13] In contrast, a double-blind study of 33 acute urticaria patients randomized to oral diphenhydramine, famotidine and cromolyn sodium showed the greatest efficacy with diphenhydramine.[14] A double-blind placebo-controlled study of 91 adult patients with acute allergic reactions (51% who had urticaria) evaluated the effects of adding intravenous ranitidine or placebo to intravenous diphenhydramine.[15] Amongst patients with urticaria, 92% of the ranitidine treated group was free of urticaria at 2 hours compared to 74% treated with diphenydramine alone which was statistically significant. Based on all of the above, it is reasonable to use H2 antagonists along with H1 antagonists in acute urticaria, though the benefit appears small.

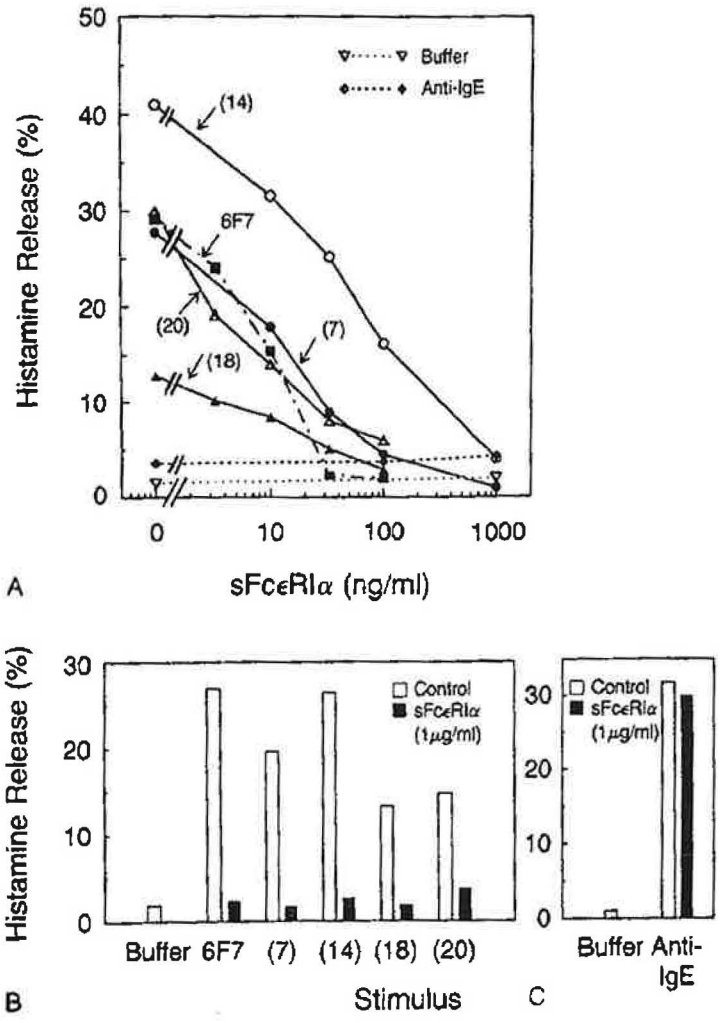
Theories on Pathogenesis of CU

In cases of urticaria due to IgE-mediated allergy (e.g. insect allergy, food allergy), the release of histamine and other preformed mediators from mast cells and basophils is easily explained. Both of these cell types have high affinity IgE receptors (FcεRI) and in sensitized individuals, allergen-specific IgE is bound to these receptors. With exposure to the culprit allergen, cross-linking of adjacent FcεRI receptors occurs, initiating a series of intracellular activation signals resulting in activation and degranulation of the mast cell or basophil. However, in the majority of CU patients, an identified allergen is not an etiology. Therefore, how do mast cells or basophils become activated to release mediators? Currently, there are several theories to attempt to explain the pathogenesis of chronic idiopathic urticaria (CIU).[16]

Autoimmune Theory of Chronic Urticaria

Links between autoantibodies and CU have been recognized for over 20 years. In 1983, Leznoff et al. reported on finding elevated titers of thyroid microsomal antibodies in 12% of 140 CU patients, suggesting an autoimmune basis for CU.[17] Three years later, Grattan et al. reported that 7 of 12 patients with CU had positive skin tests with intradermal injection of their own sera, the autologous serum skin test (ASST).[18] In 1988, the same group separated autologous sera via column chromatography from 5 ASST positive patients and found the greatest skin test response was produced from fractions in the 10-15kD range.[19] Further work by this same group indicated that the histopathology of ASST-induced wheals was similar to IgE-mediated late phase cutaneous reactions with evidence of mast cell and eosinophil degranulation.[20] Further work by Grattan and colleagues discovered an IgG serum factor capable of inducing positive ASST and histamine release from basophils along with several other properties of anti-IgE (reduction in activity by human myeloma IgE or with stripping of surface bound IgE).[21] This work culminated in their seminal paper identifying that autoantibodies to the alpha chain of FcεRI were the cause of histamine release in CU.[22]

Figure 1. Inhibitory studies of Basophil histamine release from patients with CU



Concentration-Dependent Inhibition by sFcRI of Histamine Release from Basophils from Donor 1 Induced by Whole Serum (Panel A) and IgG Fractions (Panel B) from Four Patients with Chronic Urticaria. The numbers in parentheses are the patients' numbers. The concentration of 6F7 was 30 ng per milliliter. The cells in Panel A and Panel B were not sensitized, and the cells in Panel C were sensitized with myeloma IgE. Anti-IgE antibody was used at a dilution of 1:1000 for nonsensitized cells (Panel A) and 1:50,000 for sensitized cells (Panel C). Histamine release is expressed without correction for spontaneous release.[22]

Since then, these autoantibodies have been detected in ~40% of CU subjects and these subjects are referred to as having chronic autoimmune urticaria (CAU). Additional studies have indicated that histamine release in patients with these autoantibodies is augmented by C5a.[23] However, not all antibodies detected possess the functional activity to cause histamine release. In addition, anti-IgE antibodies have been detected in 9% of CU subjects.[24]

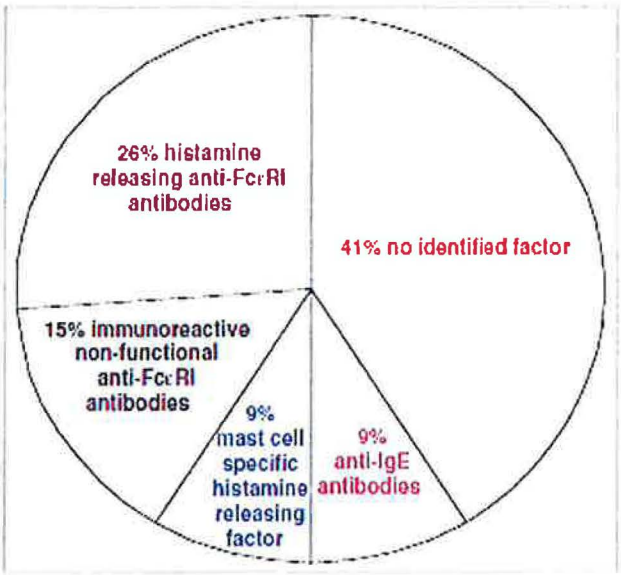


Fig. 2. Prevalence and type of autoantibodies in 78 patients with CIU.[24]

Controversies with the Autoimmune Hypothesis

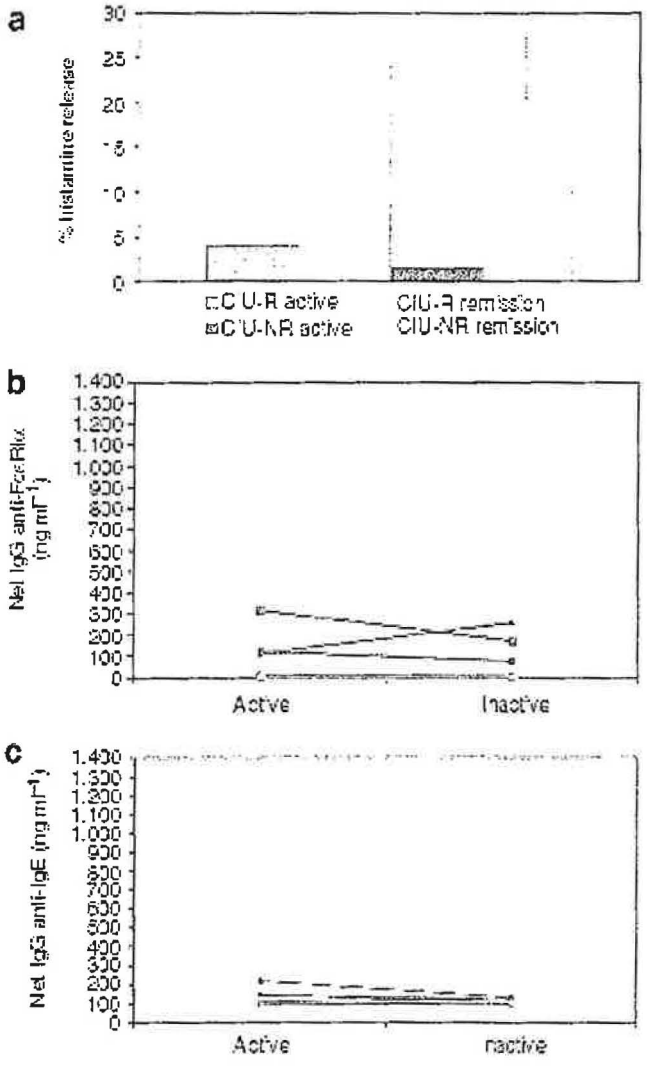
Despite the bulk of research being focused on autoantibodies in CAU, several lines of evidence shed some doubt as to the validity of this theory. Several recent studies have found serum samples from patients without CU may induce positive ASST or induce basophil histamine release.[25-27] Furthermore, few differences have been noted in clinical presentation, histology, or response to various therapies between those with CAU and idiopathic patients.[16] Finally, despite its nomenclature, there is little evidence to support that these autoantibodies are indeed pathogenic, and at the present time, data are insufficient to indicate that CAU is a true autoimmune disease.

Basophil Hyporesponsiveness Theory of CU

Another phenomenon observed in CIU is that basophils from these patients may release decreased amounts of histamine after IgE receptor activation,[28] a phenomenon noted in the 1970's. More recently Saini and colleagues have discovered that CIU patients may be separated into 2 basophil phenotypes, which they term CIU responders and CIU non-responders.[27] CIU responder basophils have a normal dose response to IgE receptor activation, similar to healthy controls. In contrast, CIU non-responders do not respond to IgE receptor activation. The

mechanism for this phenomenon may be related to elevated levels of the Src-homology 2-containing-5'inositol phosphatase (SHIP) proteins. In the basophil FcεRI signaling pathway, protein levels of SHIP–1 are inversely correlated with the release of mediators or releasability. A related phosphatase, SHIP-2, is a negative regulator of monocyte IgG receptor (FcγR) signaling. Further studies from this group showed that the prevalence of anti-FcεRIα Abs was similar in CIU subjects (regardless of basophil phenotype) and allergic and non-atopic controls.[29] In a longitudinal study of 73 CIU subjects, during disease activity, basophil phenotypes did not change. During follow-up, 6 subjects (5 non-responders) went into remission and the non-responders had increases in basophil function whereas autoantibodies had no change. These basophil phenotypes may also have some clinical relevance as basophil responders have a higher likelihood of urticaria duration > 4 years and increased itch scores than basophil non-responders.[30] Whether the phenomenon of basophil hyporesponsiveness is causal or a result of CU is still not clear.

Figure 3. Basophil phenotypes and autoantibodies during disease and in remission.[29]



Natural History of CU and Impact on Quality of Life

One of the frequent questions patients with CU will ask is "How much longer will my hives last?" This is an important question to address with patients as many feel that once they develop urticaria it will never end, particularly if their urticaria been ongoing for several months or years. Unfortunately, data on the natural history of CU are somewhat limited and based on the type of center, may not be applicable to a given clinic. A prospective study of 220 CU patients from a secondary-tertiary dermatology clinic in Amsterdam, evaluated the spontaneous remission in patients followed for 1-3 years. [31] For patients with chronic idiopathic urticaria (CIU), 47% were free of symptoms after 1 year. In contrast, only 16% of patients with physical urticaria were free of symptoms after 1 year. A retrospective study of 372 CU patients from a "supra-regional referral center" in the Netherlands demonstrated even lower rates of remission. [32] Only 29% of CU patients from this referral center were free of urticaria after 5 years and even after 10 years, only 44% were in remission. Patients with physical urticarias and more severe disease had longer durations of CU. These studies and others indicate that patients with physical urticaria tend to have a longer duration of disease. It is also important to educate CU patients that while their condition may last years, it can typically be controlled during that time and hence minimize the impact on their quality of life.

The detrimental impact of CU on quality of life is certainly obvious to most CU patients. However, the general population and most physicians view urticaria as nothing more than a minor nuisance. This may be due to the higher frequency of acute urticaria, which due to its self-limited nature may propagate a false perception that CU is a trivial condition. Formal quality of life studies have been performed which may provide a sense of reassurance to CU patients (in that their condition is significant) as well as educate other physicians regarding the impact of this condition. [33] In a study of 170 CU patients from a specialty dermatology clinic, patients with CU had impairment of quality of life comparable to severe atopic dermatitis and worse than patients with psoriasis, Behcet's, and acne. [34] Another study from the same group evaluated 142 CU patients with a more general quality of life instrument and found impairment in CU patients to be similar to those reported in a previous study of patients awaiting coronary artery bypass surgery. [35]

Etiologies of Chronic Urticaria

In the vast majority of cases of CU, an etiology cannot be determined. As discussed earlier, autoantibodies may be found in 40-50% of CU patients, but for all practical purposes, the etiology of urticaria in these CAU patients remains idiopathic. In my practice at UT Southwestern, 80-90% of CU patients I have evaluated are idiopathic. As a group, the physical urticarias are the most common etiology found in CU. Physical urticarias may often be distinguished by historical features of not only the triggering physical stimulus, but also the duration of the urticarial lesion itself. Individual physical urticaria lesions typically last between 30 minutes to 2 hours. In contrast, individual lesions of other types of CU typically last most of the day.

Table 1. Urticaria Etiologies[36]

Acute
Foods
Insect stings
Viral infection
Contact
Transfusion reactions
Medications
Chronic
Idiopathic
Autoimmune
Physical
Cryopyrinopathies*
Urticarial vasculitis
Infections?

*pseudourticarial lesions

Physical Urticarias

Physical urticarias are an extremely interesting group of urticaria/angioedema disorders. Patients with physical urticaria develop lesions in response to a wide range of environmental stimuli. The responses to these stimuli can range from mild local reactions to severe, life-threatening reactions. Patients may have an isolated type of physical urticaria, or have concomitant CIU or even multiple types of physical urticarias including those to opposing stimuli such as heat and cold.

Dermographism

Simple dermographism (dermatographia) is relatively common and occurs in 2-5% of the general population. Patients rarely seek out attention for this, as the linear wheal and flare reactions that develop from stroking the skin are not pruritic. In contrast, patients with symptomatic dermographism (factitious urticaria, urticarial dermographism) have intense pruritus, which often develops without a pressure stimulus but is certainly accentuated by minor stroking, rubbing or scratching the skin. The lesions of dermographism are typically short-lived and last only 30 minutes. The incidence of symptomatic dermographism has not been well characterized. In our clinics, it is the most common type of physical urticaria. In a series of 40 patients from a dermatology clinic in Istanbul, psychic factors (e.g. sudden changes in lifestyle, unexpected stressful life events) were found to have a triggering role in inciting dermographism in 30% of patients. [37] In addition symptomatic dermographism also occurred in 3 patients after antibiotic-induced urticaria.

The pathogenesis of dermographism is not clear. Prior studies have shown the ability to passively transfer dermographism to both humans and monkeys.[38, 39] Elevations in baseline plasma histamine have been reported in a few patients with severe dermographism with 1 of 6 subjects having systemic elevation in histamine after stroking the skin.[40]

Dermographism is easy to diagnose in the office by using a tongue blade to firmly stroke the skin and observe the area after 1-3 minutes for pruritus, erythema, and edema in a linear distribution. In our experience, the back may be a more sensitive area than the forearm in eliciting dermographism. A dermatographometer is a device that can apply a defined, reproducible amount of pressure to the skin and is primarily used in research settings. Using these tools, the threshold pressure for symptomatic dermographism is lower than that for simple dermographism.[41] Other variants of dermographism include cholinergic dermographism, cold-dependent dermographism, red dermographism, follicular dermographism, and white dermographism that may be seen in atopic dermatitis. Reports of familial dermographism are rare.[42]

Treatment of dermographism involves avoidance of tight clothing and antihistamines. Most cases of dermographism are responsive to antihistamines. UV-B phototherapy has also been reported to be helpful in some cases.

Delayed Pressure Urticaria (DPU)

DPU represents about 2% of CU. Patients with DPU develop delayed cutaneous erythema and edema often with marked subcutaneous swelling after a pressure stimulus. When this swelling involves the hands or feet, it is indistinguishable from angioedema. Pressure induced lesions typically occur 4-6 hours later, but may occur as early as 30 minutes and often last up to 48 hours. It is important to note that most patients with DPU also have concomitant CIU and angioedema, and hence many of their lesions may not be exclusively pressure-related. Furthermore, many patients with CIU can have lesions that worsen at pressure sites (e.g. beneath belts, bra straps). The latter may explain some of the reports of high incidences of DPU in patients with chronic urticaria. Historical features that aid in identifying patients with DPU include delayed urticarial lesions from shoulder straps, leaning against furniture, wearing seat belts, tight clothing, and bra straps. Swelling of the feet may result from walking, jogging or tight shoes. Swelling of the hands may result from carrying shopping bags or using a screwdriver or hammer.

The pathogenesis of DPU is unclear, however both lesional and nonlesional skin have shown increased immunoreactivity of TNF-α and IL-8 in the epidermis.[43] Interestingly, a single case report indicated the efficacy of TNF-inhibitors in a patient with DPU.[44]

The most common method of testing for DPU is referred to as the "sand bag test". This test can be performed by using 15 lbs of weight applied to the shoulder, thigh or forearm for 15 minutes and observing the site over the next 24 hours for evidence of urticaria or edema. We typically use exercising weights of 7.5 lbs attached to either end of a strap and apply this to the shoulder for 15 minutes then the thigh for 15 minutes and have the patient observe these sites or take photos. Unfortunately this technique is not standardized and in my experience many patients with histories typical for DPU may have a negative test using this methodology. Other techniques including weighted metal rods or a calibrated dermographometer have also been used. [45]

Treatment of DPU differs from other forms of CU in that it is often resistant to antihistamines. A number of other alternative agents have been reported to be efficacious in DPU including corticosteroids, dapsone, montelukast, sulfasalazine, colchicine, IVIG, and as mentioned previously TNF-inhibitors.[46, 47]

Cold Urticaria

Cold urticaria represents 5-30% of physical urticarias, being more common in colder climates. Cold urticaria patients typically have urticaria on cold-exposed areas of the body. Systemic reactions including hypotension have been associated with outdoor swimming including reports of fatalities and therefore patients need to be educated about this risk. [48] Oropharyngeal edema upon ingestion of cold substances has been reported to be a risk factor for shock-like reactions after swimming. [49] Cold urticaria is most often idiopathic but may also be associated with cold-dependent immunoglobulin diseases including: cryoglobulinemia, cold agglutinin disease, cryofibrinogenemia, paroxysmal cold hemoglobinuria, and cold hemolysis. Cold urticaria is usually diagnosed using an "ice-cube test", where an ice-cube is placed on the arm for several minutes and is determined positive if an urticarial wheal develops upon re-warming. More severe cold urticaria is usually associated with briefer times of ice contact to induce urticaria. Uncommon causes of cold urticaria including autoimmune inflammatory syndromes, cold-induced cholinergic urticaria, systemic cold urticaria and cold-dependent dermographism have negative ice cube tests.

As in other physical urticarias, circulating serum factors have been implicated in the pathogenesis. Passive transfer studies involving IgE and IgM antibodies have been demonstrated in a few patients with cold urticaria. In addition histamine, chemotactic factors, prostaglandin D_2, PAF, and TNF-alpha have been detected in the draining venous blood and skin biopsies after cold challenge.[41]

Antihistamines alone or in combination with other agents have been shown to be effective in cold urticaria. Other alternative agents include leukotriene receptor antagonists, cyclosporine, and UV phototherapy. Recently, omalizumab, an anti-IgE monoclonal antibody was reported to be successful in a child with idiopathic cold urticaria.[50]

A physical form of "desensitization" by inducing tolerance to cold urticaria by gradual immersion of the extremities into cold water at regular intervals has been effective in reducing the temperature threshold to cold urticaria.[51] Studies investigating the mechanisms of tolerance showed plasma histamine levels draining cold-challenged, clinically tolerant skin were markedly diminished compared to histamine levels obtained during cold-induced angioedema.[52] Electron microscopy of skin samples taken from tolerant skin after cold challenge revealed intact, largely normal appearing mast cells. Intradermal injection of mast cell secretagogues and vasoactive agonists into normal and tolerant skin sites resulted in similar whealing responses. Thus, these studies suggest that the state of clinical tolerance to cold stimuli is due neither to mast cell-mediator depletion or tachyphylaxis of the cutaneous vasculature to vasoactive agonists. The authors hypothesized that tolerance may be due to the induction of a specific state of unresponsiveness of mast cells to cold stimuli or possibly to depletion of a cold-induced cutaneous antigen capable of triggering mast cell degranulation. A recent report from a dermatology clinic in Germany highlights the impracticality and poor compliance with this

technique.[53] They studied 23 patients with cold urticaria who received cold bath therapy "by submerging the entire body". Patients had their mean temperature for whealing determined by arm baths, than had an initial full body bath at a higher temperature. Over several days the temperature was decreased and then patients were instructed to take daily cold baths at home. The mean threshold of whealing before therapy was 24° C, which decreased to 17° C after the cold bath therapy. At least one patient had anaphylactic shock during the treatment necessitating discontinuation. Nine of 23 patients were contacted 15 years later and only one patient was able to continue the baths for 6 months, 2 for 3 months, and the remaining 6 stopped cold baths within days to weeks of leaving the clinic. This poor compliance was observed despite the fact that all patients reported that their cold thresholds were lower for all of them while performing the cold bath therapy.

Cholinergic urticaria

Cholinergic urticaria represents approximately 30% of physical urticarias and 3-5% of CU. It occurs more often in teenagers and young adults. The prevalence of this condition is likely even higher as a prospective survey of 493 high school and college students found a prevalence of 11.2%, though most never sought medical attention.[54] The lesions of cholinergic urticaria are unique in comparison to other forms of urticaria in that they are smaller (1-3 mm) and often macular initially. They may be triggered by exercise, warm water, and emotional stress. In addition to urticaria, other cholinergic mediated symptoms such as lacrimation, salivation, diarrhea as well as wheezing may also occur. Cholinergic urticaria can be diagnosed by exercise challenge or partial body immersion in hot water (44º C).

Table 2. Precipitating Factors in Cholinergic Urticaria[54]

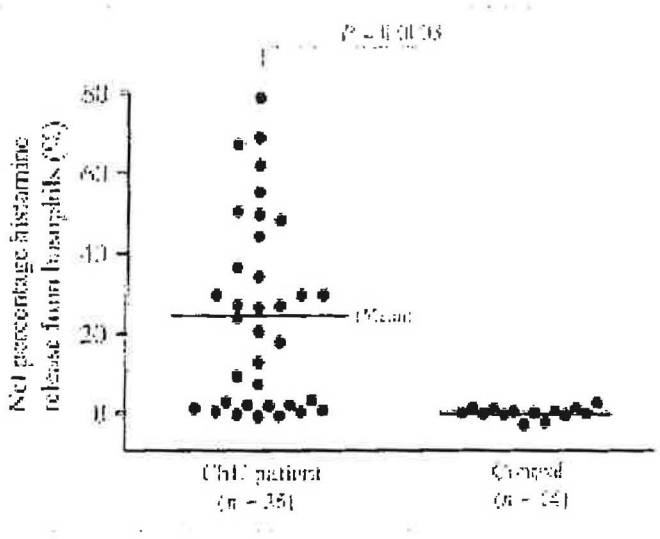
Eliciting factors	Wheals (%)	Pruritus (%)
Hot shower	69	71
Sweating	56	62
Sports	47	49
Emotional distress	20	24
Fever	9	9
Very warm meal	9	9
Alcohol	9	9
Mild exercise (e.g., climbing stairs)	5	13
Spicy meal	2	2

The pathogenesis of cholinergic urticaria is generally believed to involve an abnormal cutaneous response to cholinergic stimulation. Elevated levels of histamine in serum, increased numbers of muscarinic receptors in affected areas, and passive transfer studies to monkeys with augmentation after acetylcholine injection have all been reported.[55] Therapy with scopolamine has been reported to be successful in a case of cholinergic urticaria further supporting this concept.[56] Hypohidrosis has also been paradoxically linked with cholinergic urticaria and it has been theorized that occlusion of the pores of the stratum corneum could cause hypohidrosis and

subsequent leakage of inflammatory sweat materials into the upper dermis, resulting in urticaria.[57]

Recently, another theory has arisen to explain cholinergic urticaria in some patients, sensitivity to one's sweat. Fukunaga et al. evaluated 17 patients with cholinergic urticaria and found 11/17 had positive autologous sweat skin tests and 10 had sweat-induced histamine release from basophils. [58] The investigators described two subgroups of cholinergic urticaria based on the patient's response to autologous sweat testing. Non-follicular cholinergic urticaria is more common and patients have positive autologous sweat skin tests. Follicular cholinergic urticaria patients have weak to no response to autologous sweat skin tests but have positive autologous serum skin tests. Another group has developed a semi-purified sweat antigen and showed 66% (23/35) patients with cholinergic urticaria had elevated sweat antigen-induced histamine release from basophils.[59] Finally, a single case report suggests efficacy of using this semi-purified sweat antigen for immunotherapy in a patient with cholinergic urticaria.[60]

Figure 4: Basophil histamine release from semi-purified sweat antigen in patients with cholinergic urticaria and controls[59]



Therapy for cholinergic urticaria includes appropriate avoidance measures as well as antihistamines. Other alternative therapies for cholinergic urticaria include androgens, beta-blockers, phototherapy, and anticholinergics.[47, 61]

Solar Urticaria

Solar urticaria is a rare cause of urticaria and photodermatosis in general. A large retrospective study from a tertiary dermatology clinic in Singapore involving 21,974 urticaria patients and 270 photodermatoses found that solar urticaria represented only 0.08% and 7% of these groups respectively.[62] Urticarial lesions from solar urticaria typically appear within 5-10 minutes of ultraviolet radiation exposure. Most patients describe a sensation of burning or itching but systemic symptoms have also been reported including anaphylaxis.[63] Dermographism has been found in as many as 21% of solar urticaria patients.[64]

Solar urticaria was initially classified in 1963 by Harber et al. into 6 types based on the action spectrum (wavelength eliciting urticaria), as well as other factors including ability to passively transfer the effect via sera.[65] Leenutaphong later proposed two types of solar urticaria.[66] Type I solar urticaria patients have IgE-mediated hypersensitivity to an abnormal chromophore present only in solar urticaria patients. Type II patients have circulating IgE antibodies against a normal chromophore. Passive transfer studies of sera into normal patients are only sometimes positive in type I patients (if the abnormal photoallergen is transferred along with specific IgE) while these studies are always positive in type 2 patients because normal subjects possess the normal chromophores.

Figure 5. Type I and II Solar Urticaria (Passive Transfer and Histamine Release Assays)[63]

	In vitro activation tests†					
Solar urticaria*	Solar urticaria patient and solar urticaria serum	Normal subject and solar urticaria serum	Solar urticaria patient and normal serum	Normal subject and normal serum	Passive transfer test	Reverse passive transfer test
Type I: abnormal chromophore, normal antibody	Urticaria	No reaction	No reaction	No reaction	Variable	Negative
Type II: normal chromophore, abnormal auto-antibody	Urticaria	No reaction	Urticaria	No reaction	Positive	Negative or Variable

Phototesting is used to establish a diagnosis of solar urticaria. Since the spectrum of light varies for different patients, a variety of sources that produce different wavelengths are often employed including a UVB light source (fluorescent sunlamp), UVA light source (fluorescent black light), a visible light source (slide projector or monochromometer), natural sunlight, and even lasers. Interestingly, solar urticaria may be inhibited in some patients using "inhibition spectra" (either pre-or post irradiation) which are generally of longer wavelength than the action spectra.[63] In addition, others may have augmentation of urticaria with "augmentation spectra".

Therapies for solar urticaria include antihistamines, sunscreen, plasmapheresis, anti-malarial agents, IVIG, and cyclosporine. Phototherapy has been paradoxically very useful in a number of patients and is often referred to as "hardening". While effective, the mechanism of tolerance with this procedure is unknown. A more rapid form of hardening, "rush hardening" has also been reported to be safe and effective.[67]

Aquagenic Urticaria

One of the more unusual and rare forms of physical urticaria is aquagenic urticaria with approximately 30 reported cases in the literature[68]. Patients with this condition develop small, punctate, perifollicular wheals within minutes of direct skin contact with water, regardless of

temperature. Urticarial lesions may occur with a variety of types of water sources including melted snow, sweat, tap water, distilled water and seawater. Patients are able to ingest water without difficulty. The intensity of some patients lesions is dependent on the osmolality or ionic concentration of water.[69] Systemic symptoms including headache and respiratory symptoms have also been noted.[70] Most reported patients are in their 20's to 30's with onset usually after puberty. Dermographism has been reported in several patients.[70] Familial and localized forms of aquagenic urticaria have also been reported.

The pathogenesis of aquagenic urticaria like many other physical urticarias is incompletely understood. Shelley et al. in their initial report describing the condition proposed that a "toxic" substance is formed by water acting on the sebum or sebaceous gland and this "toxic substance" can then activate mast cells.[71] Experimental intracutaneous injections of extracts from human callus induced a burning sensation and induced basophil histamine release in two aquagenic urticaria patients but not a control.[72] Mediators including histamine, acetylcholine, and serotonin have all been postulated to have a role in aquagenic urticaria.[68]

The diagnosis of aquagenic urticaria is confirmed by a challenge with a water compress at 35° C for at least 30 minutes. Water of various temperatures can also be used as well as immersion of an extremity. To distinguish from cold urticaria, an ice cube in a plastic bag can be used which would test positive in cold urticaria but negative in aquagenic urticaria.

Therapies for aquagenic urticaria include avoidance, antihistamines, anticholinergic agents, barrier creams, phototherapy, stanozolol, and SSRI's.[68] Like other physical urticarias, physical induction of tolerance by frequent showers has been reported to modify the response to water.[73]

Vibratory Angioedema

Vibratory angioedema is another rare form of physical urticaria/angioedema where the stimulus of angioedema is vibration. After the stimulus patients complain of local pruritus, erythema, and swelling occurring within minutes and resolving in 24 hours.[55] A single case report describes a patient with delayed symptoms 1-2 hours later.[74] Triggers for vibratory angioedema include riding a motorcycle, horse or bike; handling a jackhammer; mowing the lawn; massaging and walking. The initial report of this condition by Patterson et al. indicated a hereditary condition with autosomal dominant inheritance.[75] Other subsequent reports have indicated both familial and sporadic cases.

Studies into the pathogenesis of vibratory angioedema have implicated mast cell degranulation, but passive transfer experiments have been negative.[75, 76] Further studies into the pathogenesis of this rare condition are needed.

A diagnosis of vibratory angioedema is confirmed by applying the subject's forearm to a vortex mixer for approximately 5 minutes. Like other tests in physical urticaria, this test is not standardized and controls have been shown to develop transient erythema and pruritus but usually not angioedema.[77]

Treatment of vibratory angioedema has been primarily reported with antihistamines. Physical induction of tolerance has also been reported with gradually prolonged exposure to vibration of

the hands with a maintenance vibratory "desensitization" for 5 minutes every 5-7 days and complete symptom control.[78] However, failures of vibration induced tolerance have also been reported.[79]

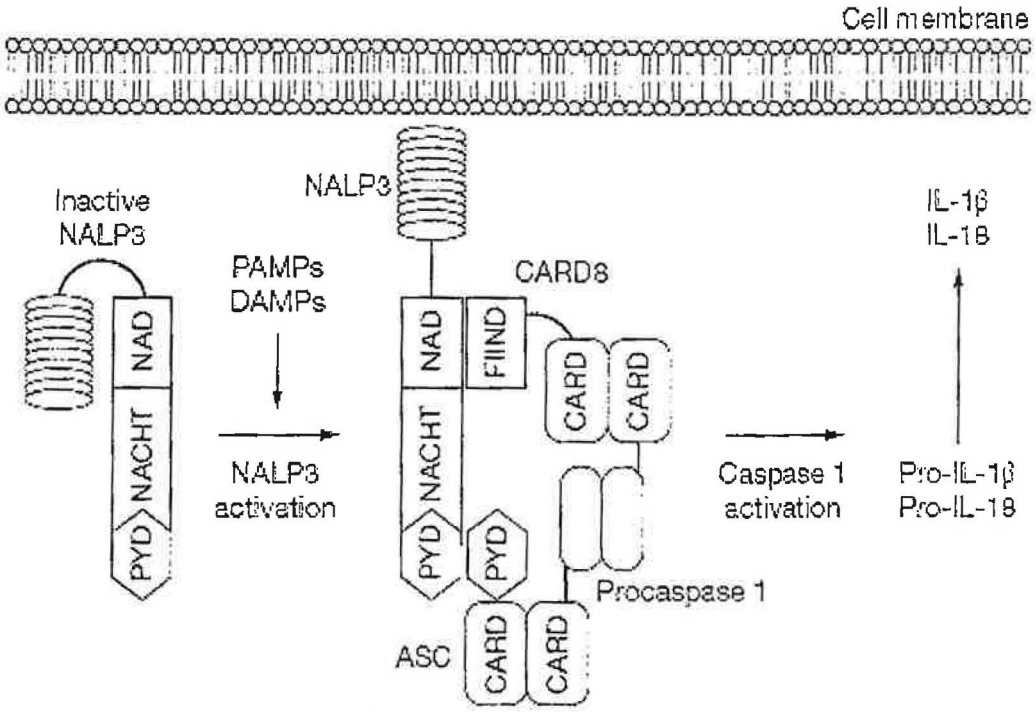
Figure 6. Testing for Physical Urticarias[36]

Physical Urticaria	Testing Method
Cold	Ice cube test
Localized heat	Test tube of water 44°C
Cholinergic	Exercise for 15–20 min Leg immersion in 44°C bath
Delayed pressure	Sand bag test: 15 lb weight for 15 min
Dermographism	Stroking skin firmly
Solar	Specific wavelength light exposure
Aquagenic	Water compress
Vibratory	Vortex for 4 min

Cryopyrinopathies (Systemic Disease with Pseudourticaria)

In the last several years, a number of well known hereditary disorders have been linked together on the molecular basis of their cytokine dysregulation. Collectively, these disorders are referred to as autoinflammatory syndromes. Unlike autoimmune diseases, autoinflammatory syndromes are not associated with antigen-specific T-cell responses or autoantibodies, but are related to disorders of innate immunity. Autoinflammatory syndromes include a number of hereditary periodic fever syndromes including familial Mediterranean fever, Hyper IgD syndrome, Pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome, TNF receptor associated periodic syndrome and Blau syndrome. Another group of autoinflammatory syndromes is characterized by mutations in the same gene known as cold-induced autoinflammatory syndrome 1 gene (*CIAS1*) but now referred to as *NLPR3* (nucleotide-binding oligomerization domain, leucine-rich-repeat family, pyrin domain containing 3). This gene encodes a protein called NALP3 (NACHT, leucine-rich repeat and pyrin domains containing protein 3), which has several other names including cryopyrin and PYPAF1. NALP3 belongs to the large family of NLR (nucleotide-binding domain and leucine-rich-repeat containing) proteins, which have key roles in innate immunity. NALP3 interacts with other intracellular proteins to form a complex called the inflammasome. This complex is crucial in innate immune responses as it detects intracellular pathogens and other danger signals.

Figure 7. The NALP3 Inflammasome.[80]



Familial cold-autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and neonatal onset multisystem inflammatory disorder (NOMID) are all due to *NLPR3* mutations and are collectively referred to as cryopyrinopathies or cryopyrin-associated periodic syndromes (CAPS). These syndromes are more appropriately considered in the differential diagnosis of CU as the lesions are not considered true urticaria. Historically, these conditions have been considered a type of urticaria, and FCAS may be confused with cold urticaria. FCAS, which used to be known as familial cold urticaria, is characterized by papular, urticaria-like lesions on exposure to cold. These lesions are distinguished from typical urticaria as they are typically non-pruritic and sometimes burning. The term "pseudourticaria" has been used to refer to these lesions.[80] In addition to cutaneous lesions, FCAS patients also have systemic symptoms including fever, chills, arthralgia, myalgias, headache, conjunctivitis, profuse sweating, nausea, and thirst. Symptoms usually begin within 1-2 hours of cold exposure including air-conditioning. The ice cube test is negative in patients with FCAS. Muckle-Wells syndrome may also have cutaneous lesions including cold urticaria and urticarial vasculitis, which is often present within the first few weeks of life. Hallmarks of this syndrome include deafness and renal amyloidosis. The most severe end of the spectrum of cryopyrinopathies is NOMID. In addition to an atypical urticarial rash, which begins early in life, patients have severe central nervous system manifestations including chronic aseptic meningitis, mental retardation, papilledema, cerebral atrophy, bony overgrowth and amyloidosis. Treatment with the IL-1 receptor antagonist, anakinra, as well as the IL-1 trap (Rilonacept), have recently been shown effective for the cryopyrinopathies. [81, 82]

Figure 8. Clinical characteristics of cryopyrinopathies.[80]

Feature	FCAS	MWS	CINCA (NOMID)
Severity	Low	Medium	High
Trigger	Cold exposure	None	None
Frequency of fever and/or rash	Usually daily symptoms with circadian rhythm	Variable: rare to daily symptoms with circadian rhythm	Variable: usually rare fever and daily rash
Joint involvement	Arthralgia	Arthralgia, arthritis	Arthralgia, arthritis, overgrowth arthropathy
Neurological involvement	None	None	Chronic aseptic meningitis (headache, possible mental delay)
Eye involvement	Conjunctivitis	Conjunctivitis, uveitis	Uveitis, papillary edema, possible optic neuritis
Deafness	No	Frequent (60–70%)	Frequent (>60%)
Amyloidosis	No	Frequent (~25%)	Frequent (~25%)
Inheritance	Autosomal-dominant	Autosomal-dominant (typical) or *de novo* (rare)	*De novo* (typical) or autosomal-dominant (rare)

Abbreviations: CINCA (NOMID), chronic infantile neurological cutaneous articular syndrome (neonatal-onset multisystemic inflammatory disease); FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome.

Urticarial Vasculitis (UV)

UV may represent 5% of CU, has a female predominance and has a peak incidence in the 4th decade of life. The clinical features of UV lesions are usually different than typical urticaria. UV lesions may be painful, tender or have a burning quality and may be non-pruritic.[83] The duration of individual UV lesions is often longer in that they last between 24-72 hours as compared to non-vasculitic urticarial lesions, which typically last less than a day. However, a recent study found that 57% of UV lesions last less than 24 hours.[84] Another distinguishing feature of UV is that the lesions may resolve with purpura of hyperpigmentation. Angioedema can also occur in UV patients. The histopathology of UV can vary but minimal criteria have proposed the presence of leukocytoclasis or fibrin deposits in the lesions, with or without red blood cell extravasation.[85]

Traditionally UV has been classified based on complement levels and other associated symptoms. Hypocomplementemic urticarial vasculitis (HUV) has been recognized as a more severe form of UV. An even more severe form of HUV has been termed hypocomplementemic urticarial vasculitis syndrome (HUVS). It is likely that these conditions are on a spectrum ranging from urticaria with minimal vasculitis to urticaria with marked vasculitis and hypocomplementemia.[83] Criterion for HUVS have been proposed requiring a major criterion and 2 minor criteria.[86] The major criteria is urticaria > 6 months duration and hypocomplementemia. Minor criteria include dermal venulitis, arthralgia/arthritis, uveitis/episcleritis, mild glomerulonephritis, recurrent abdominal pain, or a positive C1q precipitin test with a suppressed C1q level. Exclusion criteria include elevated anti-DNA antibody titer, high titer ANA, hepatitis B virus antigenemia, decreased C1 esterase inhibitor level, or an inherited complement deficiency.[83] If patients do not meet these criteria but have hypocomplementemia, they are referred to as HUV. Systemic symptoms may also occur in UV

patients. HUVS is frequently associated with COPD and ocular inflammation. Some authors consider HUVS as an atypical form of SLE, however COPD and uveitis are not common manifestations of SLE and most consider it separate from SLE.

Figure 9. Clinical features of UV.[83]

Occurence	Cutaneous features	Systemic features
Common	Erythematous urticarial papules and plaques (wheals), angioedema, dermographism, annular erythema	Musculoskeletal: arthralgia, arthritis
Less common	Urticarial lesions with residual hyperpigmentation or purpura	Respiratory: cough, dyspnea, hemoptysis, COPD, asthma, pleural effusion Renal disease: hematuria, proteinuria, glomerulonephritis Gastrointestinal: substernal pain, abdominal pain, nausea, vomiting, diarrhea
Rare	Erythema multiforme-like lesions, livedo reticularis, Raynaud's phenomenon, laryngeal edema	Cardiac: pericarditis, pericardial effusion, cardiac tamponade Ophthalmologic: conjunctivitis, episcleritis, uveitis, geographic serpiginous choroidopathy, visual loss Other: fever, splenomegaly, lymphadenopathy, cold sensitivity, reversible tracheal stenosis
Very rare		CNS: pseudotumor cerebri, cranial nerve palsies, aseptic meningitis Miscellaneous: transverse myelitis, cardiac valve disease, optic atrophy, Jaccoud's syndrome (chronic posttheumatic fever arthropathy), peripheral neuropathy, pleuritis

Laboratory findings in UV may include an elevated ESR and positive ANA. In HUV or HUVS, depressed C1q, C3, C4 levels and low CH50 are present. Anti-C1q antibodies are reportedly present in 100% of patients with HUV/HUVS but may be seen in other diseases including Felty's syndrome, SLE, Sjogren's syndrome, and MPGN.[87]

UV is most commonly idiopathic but may be associated with SLE or Sjogren's syndrome. There are several other more rare reported causes and diseases associated with UV including infections, medications, paraproteinemias, hematologic diseases, complement deficiencies, physical urticaria and malignancies.(Figure 10) Patients with UV are often refractory to antihistamines and numerous other agents have been used with variable efficacy.

Figure 10. Causes and Associations of Urticarial Vasculitis[85]

- Common
  - Idiopathic
- Less common
  - Connective tissue disease
    - Systemic lupus erythematosus, Sjogren's disease
  - Serum sickness
- Rarer
  - Drugs
    - Diltiazem, cimetidine, procarbazine, potassium iodide, fluoxetine
  - Infections
    - Hepatitis B, hepatitis C, infectious mononucleosis, Lyme disease
  - Complement deficiencies
    - Complement deficiencies C3 and C4, nephritic B factor
  - Immunoglobulin abnormalities
    - IgG macroglobulinemia (Schnitzler's syndrome), IgG gammopathy, IgA myeloma, cryoglobulinemia
  - Hematological diseases
    - Leukemia, lymphoma, polycythemia, post-Hodgkin's disease treatment
  - Physical urticarias: cold urticaria, solar urticaria
  - Others: inflammatory bowel disease, Muckle-Wells syndrome, Cogan's Syndrome, Jaccoud's syndrome, malignancy

Infectious Causes of Urticaria

Numerous case reports and case series have suggested that various localized or systemic infections may cause chronic urticaria. Certainly, common childhood viral infections and Hepatitis B are a known cause of acute urticaria. The evidence for infectious causes of CU spans from a lack of evidence at best, to evidence that is considered controversial. In 1971, James and Warin suggested a link between *Candida albicans* and CU based on observations that 36% of their patients had positive skin tests to *C. albicans*.[88] More recently a similarly sized study found comparable skin test reactivity to *C. albicans* amongst CU patients and controls but 13% CU patients had elevated in vitro specific IgE to *C. albicans* but none of the controls had positive in vitro assays.[89] The relevance of these findings is unclear but in my experience CU patients do not reliably respond to anti-fungal agents.

The most recent infectious agent to gain attention as a causative factor in CU is *Helicobacter pylori*. Studies have been conflicting on whether therapy for *H. pylori* has a beneficial impact on CU with several studies showing positive effects[90-93] and many others with no impact.[94-97] Only a few double blind placebo-controlled studies have been performed, one that indicated no effect of *H. pylori* treatment on CU[96], and another that claimed benefit but the results were not statistically significant[98]. In a recent commentary on his experience with 10,000 CU patients, CU expert Allen Kaplan comments on *H. pylori* testing in CU: "Nevertheless, I have never ordered the test, and see no reason to do so. If one waits long enough, this idea will disappear." My own impression of the

role of *H. Pylori* in CU is similar.

Differential Diagnosis of Urticaria/Angioedema

To experienced physicians, urticarial lesions are usually readily identifiable as such. However, many patients and physicians will mistakenly identify rashes as being "hives" when in fact they are not. In an inpatient setting, the most commonly confused rash is the drug exanthem or "maculopapular rash". These lesions are pruritic often beginning as macules that can evolve into papules and eventually may coalesce into plaques. Drug-induced exanthems typically involve the trunk and spread outward to the limbs in a bilateral symmetric pattern. In contrast to urticaria, the drug exanthem is typically composed of very fine papules, while urticarial lesions are usually larger, often a few centimeters in diameter or larger. Drug exanthems may also scale whereas urticaria resolve without scaling or pigmentary changes. Contact dermatitis, and other forms of eczema can occasionally be mistaken for urticaria. Eczema is often scaly, or weepy depending on the stage and the individual lesions persist for many days. Bullous pemphigoid may have an urticarial phase to it, but these lesions also tend to be more persistent. Other cutaneous diseases that may be confused with urticaria include fixed drug eruption, cutaneous lupus erythematosis, and Sweet syndrome.[99] As discussed earlier, pseudourticarial lesions may be seen in the cryopyrinopathies. In the presence of both urticaria and angioedema, few conditions other than UV are mistaken for CU.

Evaluation of Patients with CU

The most important diagnostic aid in evaluating patients with CU is a detailed history. Most physical urticarias can be suspected based on the history and if suspected, testing for physical urticaria can be performed. UV similarly has many features that differentiate it from CIU. The cryopyrinopathies are rare and their inheritance pattern and other clinical features easily separate them from CIU patients. Autoimmune urticaria can only be diagnosed by serologic testing for autoantibodies or more specialized tests evaluating activation markers on basophils. However the presence of autoantibodies to FcεRI has little predictive relevance to prognosis or treatment but may be helpful in stopping a patient from other fruitless searches for an etiology to their CU. A complete review of systems is essential in identifying any other systemic symptoms that would warrant a more directed laboratory evaluation.

In the absence of a suggestive history, which is most often the case, what diagnostic tests should be performed in the evaluation of patients with CU? This is the subject of debate and controversy amongst urticarial specialists. In clinical practice, there is a wide spectrum of evaluations ordered by practicing allergists ranging from no testing to extensive evaluations costing thousands of dollars. A systematic review of several studies addressing this issue helps to provide some recommendations based on the evidence. Kozel and colleagues performed a literature review on published series with > 50 patients that evaluated diagnostic laboratories in CU. [100] They evaluated 29 studies involving 6462 patients. Overall no relationship was found between the number of identified diagnoses and the number of laboratory tests performed. The range of identified diagnoses varied widely between studies as well as their causes. When evaluating those studies that excluded physical urticaria, the percentage of diagnoses found was the lowest (1-20%). In only 1.6% of patients was an internal disease considered being the cause of CU, the majority of these (57%) were cutaneous vasculitis. Most authors concluded that

history is very important (10 studies), that routine laboratory tests are of little value (13 studies), and that laboratory tests are only useful on the basis of the history (7 studies).

My opinion on diagnostic testing is similar to the results of the aforementioned review. In the absence of a suggestive history (including a complete review of systems), I do not perform any routine laboratory tests on CU patients. I question patients regarding any specific triggers they are concerned about at subsequent visits and can obtain appropriate testing as needed. If patients fail to respond to antihistamine therapy, I obtain laboratories for TSH and thyroid autoantibodies. While controversial, treatment with suppressive doses of thyroxine may be beneficial in patients with CAU with thyroid autoantibodies. [101] In some patients, I do obtain autoantibodies to FcεRI, but this is primarily to help in concluding the work-up of their CU. In patients I suspect have UV, complement levels, ESR, ANA and skin biopsies are obtained, but I certainly do not advocate ANA testing for all CU patients. It is important to note, that skin testing for aeroallergen or food sensitivity is not indicated in the evaluation of CU, despite this being a relatively common practice amongst allergists.[102, 103]

Management of CU

Reassurance

One of the most important yet, often overlooked management strategies for a CU patient is reassurance. Many patients referred to me from other specialists have not received the necessary reassurance and education on their disease and hence have a great deal of anxiety regarding their condition. Important messages for the patient include that CU is a relatively benign disease and even with associated angioedema, is not a fatal condition. In this regard, I rarely prescribe self-injectable epinephrine in CIU patients with angioedema, as it tends to send the wrong message that their angioedema puts them at high risk for fatal laryngeal edema when in fact this is not the case. Nonetheless there are those patients that feel safer having self-injectable epinephrine and in these cases a prescription may be reassuring. At the first visit I will instruct patients that while we rarely find a cause of CU, it has a self-limited course and importantly, can usually be successfully managed in a way that will not significantly impair their quality of life.

Non-Pharmacologic Therapies

While many CU patients observe that certain non-specific triggers aggravate their urticaria, it is important to discuss these with CU patients. Non-steroidal anti-inflammatory drugs (NSAID) may exacerbate urticaria in a significant percentage of CU patients and patients should be counseled on this possibility. Certainly if patients require NSAID therapy and do not observe any flares in their CU, prohibition of these agents may not be necessary. Heat is another common trigger for CU patients as is tight clothing, the latter more of a problem for patients with DPU. Narcotics may also exacerbate some CU patients. Pseudoallergen free diets are often recommended by European authorities but are rarely recommended in the United States based on minimal evidence of their efficacy. These diets are very difficult to adhere to but are easy to recommend, particularly if the patient is convinced additives are causing their CU. In my experience, these diets are an effective way of disproving this belief in the occasional "additive-induced urticaria" steadfast believer.

Antihistamines in CU

Since nearly all symptoms of urticaria are primarily mediated by H1-receptors located on nerves and endothelial cells, it is logical that H1-antagonists are the mainstay of treatment for CU. Both first generation and second generation antihistamines have been used in the treatment of CU. A recent international consensus meeting on urticaria concluded, "considering their good safety profile, second-generation antihistamines must be considered as first line symptomatic treatment for urticaria". [104] They assessed data on second generation antihistamines for urticaria as having a level of evidence of 1++ with a grade A recommendation. Comparative clinical data on second-generation antihistamines in CU show similar efficacy overall. Different individual responses to second generation antihistamines are accepted as expert opinion. [104]

It is well-recognized that many patients with CU may not respond to typically recommended doses of second generation antihistamines and higher doses may be required.[105] Studies evaluating cetirizine in doses ranging from 10-30 mg a day showed conflicting results with one study suggesting benefit from increased dosing [106] and another without demonstrable benefit. [107] The aforementioned international guidelines recommend using second-generation antihistamines at doses up to four-fold higher prior to considering alternative therapies but the level of evidence was low. In my experience, higher doses of second-generation antihistamines do improve some patients with CU but that increasing beyond twice the recommended dose is rarely beneficial.

First generation antihistamines also have a role in CU. While sedation, lack of perception of sedation, and development of tolerance to sedation with first-generation antihistamines are well known concepts, data in regards to CU patients is sorely lacking. While the degree of impairment varies amongst first-generation antihistamines, as a group they cause significantly greater impairment of cognition and psychomotor function than second-generation antihistamines.[108] Sedating antihistamines are often recommended to be dosed as a single nocturnal dose in an attempt to reduce daytime impairment.[109] Data are lacking regarding whether this approach does reduce daytime somnolence especially when given chronically to patients with CU. Reassuringly, studies evaluating subacute use of first generation antihistamines have shown tolerance to performance impairment after 3-5 days of therapy.[110-112] Kaplan has been a proponent of using hydroxyzine, typically at doses of 50 mg four times daily and has recently discussed why sedation is over-emphasized in CU patients treated with first-generation antihistamines.[113] He also states that "I discontinued first-generation antihistamines in about 2% of the 10,000 patients treated because of sedation; the remainder had no complaints, and I know of no serious automobile accidents." I will prescribe hydroxyzine or doxepin in CU patients who have failed higher doses of second-generation antihistamines. However, I typically prescribe them as a single dose at bedtime and gradually increase the dose over time (in weekly increments) based on tolerance to sedation. In my experience, patients rarely derive added benefit from doses higher than 150 mg a day of either drug. While sedation is certainly a problem, many patients can tolerate these drugs without adverse effects. I also recommend obtaining an electrocardiogram to monitor for QT prolongation in elderly subjects requiring more than 75 mg a day of first-generation antihistamines.

H2-receptor antagonists have also been widely used for CU. The majority of studies evaluating the efficacy of these drugs in CU were with cimetidine. Cimetidine is an inhibitor of a number of cytochrome p 450 isoenzymes including those that are involved with metabolism of first-

generation antihistamines. Plasma concentrations of hydroxyzine were higher in combination with cimetidine than with hydroxyzine alone. [114] This pharmacologic interaction may explain the perceived benefit of H2-antagonists in CU. My own experience suggests that it is extremely rare for patients with CU to derive additional benefit from H2-antagonists and that discontinuing them typically does not cause flares of CU.

Alternative Agents for CU

Despite the use of antihistamines, some patients with CU remain refractory to this therapy. I define patients with antihistamine resistant CU by having one of two features: 1) failure to control CU despite high doses of antihistamines and/or 2) patients intolerant of high dose antihistamine therapy. While typically systemic corticosteroids are employed by many, this is not a recommended approach. Though systemic glucocorticoids are perceived to be effective in CU, interestingly controlled data are lacking to demonstrate their efficacy. More importantly, toxicity of systemic glucocorticoids is nearly inevitable in almost all patients treated for CU as doses requiring control are well above physiologic doses.

Table 2. Second-Line Alternative Agents for Refractory CU

Drug	Level of Evidence
Leukotriene Modifiers	Ib
Dapsone	IIb
Sulfasalazine	III
Hydroxychloroquine	Ib
Colchicine	III
Calcineurin Inhibitors	Ib
Mycophenolate	IIb
Omalizumab	III

Category of Evidence[115]

Ia: evidence for meta-analysis of randomized controlled trials

Ib: evidence from at least one randomized controlled trial

IIa: evidence from at lease one controlled study without randomization

IIb: evidence from at lease one other type of quasi-experimental study

III : evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies

IV : evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

A number of alternative agents are available to treat refractory CU. Some of the agents are immunomodulatory, some possess immunosuppressant activity, others have various anti-inflammatory effects, and many work through unclear mechanisms of action. We have recently published a two-part evidence-based review on the efficacy of alternative agents for CU. [116 117] Table 2 lists the most reasonable alternative agents to consider for patients with refractory CU

and their level of evidence. [115] The presence of autoantibodies to FcεRI does not have any consistent predictive effect of response to any alternative agent. For patients with antihistamine resistant urticaria, I will typically start with medications such as leukotriene modifiers, dapsone, sulfasalazine, or hydroxychloroquine. For patients failing these alternative agents, calcineurin inhibitors are typically effective. I prefer tacrolimus as in my experience, patients have less adverse effects compared to cyclosporine. Mycophenolate mofetil has even less adverse effects than calcineurin inhibitors but the published experience with this agent is currently less robust. Omalizumab may be another attractive option for allergists given their familiarity with this agent. While the current evidence for omalizumab in CU and idiopathic angioedema is limited to small case reports and series [118-120], my own anecdotal experience has been very positive in an albeit small number of CU patients.

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