

Urticaria and angioedema: an overview

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Urticaria is a common clinical problem for patients and physicians. Most episodes of urticaria last only a short time and are not a major clinical problem. Persistent or frequent episodes of urticaria are difficult to evaluate and treat. Chronic urticaria was referred to as a “vexing problem” in a landmark review almost a half-century ago [1], and it remains so today. Its symptoms suggest an allergic reaction, yet often the disease process is autoimmune or idiopathic in nature. Chronic urticaria often responds incompletely to antihistamines, and patients are uncomfortable and frustrated by the chronic pruritus. Some cases respond to systemic steroids, but the potentially serious side effects associated with these medications preclude their safe chronic use.

It is hard to improve on the clinical description of this condition by Heberden, published in the 18th century. He described, “The little elevations upon the skin in the ‘nettle’ rash often appear involuntarily, especially if the skin be rubbed, or scrubbed, and seldom stay many hours in the same place, and sometimes not many minutes. There is no body exempt from ‘them’ and by far the greatest number experience no other evil from it besides the intolerable anguish arising from the itching . . .” [2]. Urticaria also has been described in Chinese medicine as early as the seventh century and is known as *Fong-Tzen-Kwai* (“wind-rash-patch”) [3]. The source of these symptoms was identified in 1877 by Paul Ehrlich, who described the *mastzellen*, so-named for the granules with which they are “stuffed” [4]. These granules are packed with a variety of vasoactive mediators, most notably histamine, which cause the vasodilation, capillary leak, and pruritus characteristic of urticaria. Urticaria was

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named for the stinging nettle plant (Latin, *urtica*), which is now known to contain histamine [5].

Epidemiologic studies place the lifetime incidence of urticaria at about 15% to 25% [1,6], and it is more prevalent in middle-aged women [7,8]. Patients often complain that their symptoms are not taken seriously enough, and a self-rated quality-of-life survey of patients with chronic urticaria showed responses similar to responses from patients with ischemic cardiac disease awaiting bypass grafting. Among patients with urticaria, the subgroup with delayed-pressure type symptoms reported significantly greater discomfort on several important measures [9]; patients with urticaria and angioedema did not report poorer quality of life than those with urticaria alone [10]. Another survey demonstrated significantly poorer self-assessed quality of life among patients with chronic urticaria when compared with patients with respiratory allergies [11]. Patients' perception of the relative lack of importance accorded to urticarial symptoms, by some healthcare professionals, is validated by the fact that acute urticaria was ranked as number 636 and chronic urticaria ranked number 684 on an ordered list of 745 diseases for funding by the Oregon Health Plan, both of which were below dermatophytosis and the initial cutoff point (number 606) established for funding treatment [12].

It is not unusual for patients with chronic urticaria to undergo intensive evaluation, often including extensive laboratory tests of blood and other body fluids or even roentgenologic studies that are ordered by multiple specialists, looking for the cause of the symptoms. Most of these cases are idiopathic in nature, however, and unfocused laboratory evaluations are of little use [13–16]. The best test to identify most patients with a specific underlying cause (eg, physical trigger, allergen, systemic disease) is the taking of a careful and detailed history and performance of a physical examination by a specialist who is knowledgeable in urticarial disease. Patients should be questioned thoroughly about all medications, including asking about products that most individuals may not consider to be medications or may not volunteer information about unless asked specifically, such as over-the-counter preparations, herbs, supplements, vitamins, and so-called “traditional medicines” [1]. For example, a case series of allergic reactions to echinacea has been published [17]. According to data from the Australian Adverse Drug Reactions Advisory Committee (a voluntary reporting system), urticaria or angioedema also has been associated with use of the following products as herbal treatments: cranberry, feverfew and willow, garlic, ginger, glucosamine, horseradish, hypericum, phytoestrogen, propolis, royal jelly, and valerian, among other agents [17]. In the authors' experience, a common trigger in chronic idiopathic urticaria is the frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs). Patients rarely volunteer this information about such use unless directly asked.

Similarly, all products that are applied topically or otherwise contact the skin must be identified, including topical medications, soaps, cosmetics, toiletries, lotions, creams, detergents, fabric softeners, hair dyes, and nail products. The authors have seen several cases of urticaria that apparently were related to

the use of homemade or craft soaps. The popularity of using natural essential oils from herbal sources (for coloration and fragrance) in soaps, shampoos, and other toiletries has resulted in cases of contact dermatitis or urticaria [18]. Sometimes, herbal products that are used to treat skin conditions, such as melaleuca (tea tree oil), can cause cutaneous allergy [19,20]. Some patients with chronic urticaria are found to be using a panoply of medicaments, ointments, unguents, emollients, and other substances on the skin, likely confounding the underlying condition with a form of urticaria medicamentosa. Special concerns in this regard include topical antipruritics, topical anesthetics, and herbal products and fragrances [21–23]. These products, along with neomycin, nickel, and thimerosal, are common contact allergens [24].

Allergy and dermatology: a multidisciplinary approach to urticaria

Symptoms of urticaria lie at the interface between the fields of allergy and dermatology. Some patients seek specialty care first from a dermatologist, whereas others present first to an allergist. Both specialties have much to contribute to the care of patients with challenging urticaria [25]. Consultants in both fields are expert in obtaining detailed information from patients with urticarial symptoms in regard to possible allergic exposures, including foods, medications, contact allergens, and airborne allergens. Obtaining this information often involves extensive questioning about possible exposures related to work, hobbies, pets, and other environmental issues. Certain forms of specialized testing, if indicated, may be more readily available from an allergist (allergy skin prick testing, such as that for particular suspected food allergens) or a dermatologist (patch testing for contact allergens or urticants, skin biopsy to rule out urticarial vasculitis). Certain less common conditions, such as hereditary angioedema or idiopathic angioedema and anaphylaxis, more often may be managed by allergists, whereas vasculitic syndromes or urticaria and angioedema complicating connective tissues diseases (eg, lupus) may involve formal rheumatologic care. Some patients with chronic urticaria, particularly those with severe or persistent disease, may significantly benefit from both allergy and dermatology evaluation and management.

Henderson reviewed data from the National Ambulatory Medical Care Survey from 1990 through 1997 and found an average of 1.1 million outpatient visits per year to all physicians for urticaria of any sort [25]. At those visits, H₁ antihistamines were used in 56%, whereas a systemic corticosteroid was prescribed in 14%; medications with published support but off-label use made up 12%. Dermatologists (21%) accounted for a much larger proportion of visits than allergists (12%), although the bulk of visits were to primary care physicians (59%). Each allergist saw a mean of 47 patients with urticaria per year. Significant differences in medication management were noted; allergists had the lowest rates of systemic steroid use (6%), and internists, who most often prescribed steroids as monotherapy, had the highest rates (29%).

Allergists were also the most likely to use an off-label agent [25]. Practice guidelines have been published by allergists in the United States [26] and dermatologists in the United Kingdom [27] to address special diagnostic and management issues in the care of patients with urticarial disease.

Differential diagnosis and classification

Because urticaria is a sign (when observed by the clinician) or symptom (when described by the patient), classifying patients with urticarial disease is crucial to developing a meaningful and useful differential diagnosis. Defining terms is a helpful place to begin: Urticaria, as described in detail earlier, are raised (edematous) pruritic papules, that may be pink or red, although classically they are pale wheals surrounded by an erythematous flare. These lesions usually are discrete, round or oval in shape, and of several millimeters to a few centimeters in size; they less commonly are irregular, serpiginous, or gyrate or are of any size [28]. If the lesions are linear, they are usually not urticaria per se, but dermographism triggered by scratching the skin. In severe disease, many lesions may coalesce to form huge confluent plaques. The lesions are notable among skin conditions for their evanescence, usually lasting minutes to hours, and may occur anywhere on the body [1]. Occasionally, a seasonal, menstrual, or diurnal pattern is noted [8]. Lesions that are painful (more than pruritic), last more than 24 hours, leave permanent pigmentary change, are nonblanchable (such as by diascopy), form vesicles, or are accompanied by purpura suggest urticarial vasculitis [29–32]. Patients are often uncertain if individual lesions last more than 24 hours, and it can be helpful to ask patients to circle particular wheals and observe them over time to clarify this important point [28]. One publication suggested that skin surface microscopy (capillaroscopy, or dermoscopy), a more sophisticated form of diascopy, may be sensitive and specific for distinguishing vasculitic lesions from more common and benign urticaria without the need for an invasive biopsy procedure [33]. The shape, location, pattern, and other characteristics of the lesions may suggest subtypes of urticaria, such as the diffuse, monomorphic, small (approximately 0.5-cm diameter), “pencil-eraser” lesions of cholinergic urticaria; or the large and extensively indurated lesions found on the exposed extremities (especially the legs) of patients with cold-induced urticaria [34,35]. As mast cells exist in the mucosa as well as the skin, gastrointestinal symptoms from urticaria or angioedema of the gut can accompany the cutaneous symptoms [1,35]. It is not clear why this occurrence seems to be the exception, not the rule, in these cases. Kaplan has presented evidence that C5a is an important co-activator of mast cells in autoimmune urticaria and has suggested that the distribution of receptors for C5a on cutaneous, and not mucosal, mast cells may explain the rarity of these reports [36].

The term angioedema is used for urticarial lesions that form in deeper layers of the skin (deep dermis, or subcutaneous and submucosal layers), commonly in

the region of the head and neck, although they can occur virtually anywhere [35]. This syndrome is distinct from the angioedema seen in hereditary or acquired angioedema and that seen as a complication of use of angiotensin-converting enzyme (ACE) inhibitors, in which the swelling is thought to be driven by excess kinin activity [37]. Angioedematous lesions that sometimes accompany urticaria, but infrequently present without urticaria, are characterized by extensive swelling and induration. They generally have substantially less (or no) pruritus compared with urticarial lesions. These lesions tend to be somewhat longer lasting than urticaria and can be accompanied by a sense of burning, pressure or tightness, or a dull ache in the affected area. Identifying and distinguishing angioedema from urticaria is important. First, along with anaphylaxis, angioedema is the only truly potentially life-threatening aspect of this condition, should the airway be affected. Patients who have experienced potentially life-threatening angioedema should maintain ready access to epinephrine and be knowledgeable of its indications, administration, and relatively brief duration of effect [6,26]. Second, approximately 50% of patients with urticaria have angioedema, and these patients tend to have more severe disease, more prolonged disease, and symptoms that are less responsive to therapy, as compared with patients with urticaria alone [14]. Finally, although patients with angioedema alone are uncommon, the differential diagnosis in these cases is different (including hereditary angioedema, acquired or paraneoplastic angioedema, idiopathic angioedema or anaphylaxis, and drug reactions—especially ACE inhibitors or NSAIDs) [38].

Classification of the urticarial diseases begins with duration and frequency. Although 6 weeks of daily or nearly daily symptoms has been chosen as the arbitrary dividing point between acute and chronic urticaria, it has been useful in developing an appropriate differential diagnosis, as common causes of acute and chronic urticaria are different [39]. Although the focus in this issue is primarily on chronic urticaria, it is worthwhile to briefly discuss acute urticaria. Acute urticaria is more common in young adults and children and most often is caused by an allergic reaction (to a food, drug, insect sting) or an acute infection, particularly viral infections [1]. Few cases are referred to specialty care, and many cases probably are identified and managed by the individuals themselves without seeking any formal medical care. Sometimes patients seek confirmatory testing from an allergist about a suspected food trigger, or an allergy evaluation may be sought if a particular medication is suspected and there are limited or no therapeutic alternatives. Some medication reactions may not be truly allergic but may be caused by nonspecific mast-cell-releasing, or anaphylactoid, properties of the drug. Common drugs with these properties include opiates, vancomycin, and radiocontrast media (especially high-osmolar or ionic agents) [30]. Other causes of acute urticarial reactions include scombroid fish poisoning, allergy to insect envenomation, and transfusion reactions. A specific cause may not be identified in up to 50% of cases of acute urticaria [39]. Once symptoms have persisted on a frequent basis for more than 6 weeks, the patient is considered to have chronic urticaria. Relevant physical or environmental triggers should be identified, and systemic conditions that are associated with urticaria should be con-

sidered, although identifying specific causes is less likely with this condition than with acute urticaria.

The two largest subgroups of chronic urticaria are the physical urticarias, in which physical stimuli initiates the formation of lesions, and autoimmune urticaria, which is caused by functional autoantibodies to the high affinity receptor for IgE (Fc ϵ RI) or (less commonly) to IgE itself. Previously, cases of chronic urticaria without identified physical or environmental causes and without associated distinct systemic diseases had been grouped under the heading of idiopathic urticaria. Because an autoimmune process has been identified in 30% to 40% of these cases, offering at least a partial explanation of the disease, this grouping is no longer satisfactory. Grattan has suggested using the term “common urticaria” (as distinct from physical urticaria and urticarial vasculitis) to include idiopathic cases and cases caused by allergy, pseudoallergy, or autoimmunity [40]. Grattan restricts the use of the term “idiopathic” to cases in which no specific cause, including autoimmunity, is known or suspected.

The physical urticarias are reviewed by Dice later in this issue [41]. These conditions are notable for tending to be more persistent and less responsive to therapy than the idiopathic form of chronic urticaria [8,42]. This fact makes identification and minimization of physical triggers important. One large survey found that physical urticarias accounted for about 17% of cases of chronic urticaria (9% dermatographic, 5% cholinergic, 3% cold, and others) [14]. The most common and straightforward of these triggers is dermatographism (also called dermographism), in which wheals can be “written on the skin” by simple stroking or scratching. This common condition has a prevalence of approximately 4% to 5% [43]. Many individuals with mild dermatographism and no spontaneous urticarial symptoms probably do not seek specific medical care for this condition and may use over-the-counter antihistamines for symptomatic control. Frequently, patients with other types of chronic urticaria, or idiopathic urticaria, also may have a dermatographic component to a greater or lesser degree, presumably reflecting instability of the mast cells for degranulation. Patient history may suggest this trigger, and it readily can be confirmed by scratching the skin and observing a wheal-and-flare response. The occurrence of erythema alone after a physical stimulus, without whealing, does not meet this criterion [43]. Calibrated dermatographometers (Hook & Tucker, Croydon, England) have been used to standardize this stimulus [39,44], but they no longer seem to be readily available in the United States.

Cholinergic urticaria often is included in the physical urticarias, although this condition may be caused by a neural mast cell trigger [45]. These patients usually have a distinctive clinical presentation of diffuse erythema and elevated and pale monomorphic urticarial lesions of a few millimeters in diameter (so-called “pencil-eraser” lesions) on performing exertion that is sufficient to cause sweating [46]. The pruritus is reported to be intense. This condition rarely is associated with anaphylaxis. Because the trigger is believed to be related to the cholinergic innervation associated with the sweating reflex, overheating in the absence of exertion (eg, spicy foods, emotional stress) also may trigger these

symptoms [5]. Although exercise testing (such as with a treadmill) is not routinely available to most allergists or dermatologists, some have tried intradermal injections of cholinergic agents as a substitute test (although it is significantly less sensitive) [45–47].

Cold urticaria is another relatively common physical urticaria and is discussed in detail by Wanderer and Hoffman elsewhere in this issue [48]. There are a variety of specific subtypes of cold urticaria, including familial and nonhereditary types. Confirmatory testing should be sought with the use of an ice-cube test, whereby ice is applied to the skin for several minutes, and this area is observed for the development of urticaria.

Delayed pressure urticaria is an uncommon physical urticaria, but is a significant clinical problem. This condition is discussed in more detail by Lawlor and Black elsewhere in this issue [49]. In this subset of patients, a significant amount of pressure (particularly if deep or prolonged) on the skin results in symptoms after a delay of a number of hours. Although urticaria occurs, typically the symptoms are more angioedematous in nature. Some investigators make a distinction between simple urticarial Koebnerization at sites of pressure, commonly seen in many type of urticaria, and true delayed pressure lesions [50,51]. These symptoms also differ in being less pruritic and more painful and prolonged. In severe cases, the symptoms may seem to be more inflammatory and may overlap with the spectrum of urticarial vasculitis [32]. Diagnosis can be confirmed by hanging a weight over an arm or leg (such as a 15-lb weight for 15 minutes) using an unpadded strap [51]. Because symptom onset is delayed for several hours, patients need to return for observation after this usual period. Vibratory urticaria, which may be seen in jackhammer operators or others who are exposed to similar triggers, probably represents a variant of delayed pressure urticaria and may be tested using a laboratory vortexing machine [52,53].

Other rare types of physical urticaria have been reported, such as solar urticaria and aquagenic urticaria [54,55]. Particular ingestants (eg, foods, medications, herbs, supplements) or contactants (eg, soaps, lotions, detergents, cosmetics, toiletries, hair or nail products, latex) are rare causes of chronic urticaria. New research (discussed in detail later in this article and reviewed by Grattan later in this issue) [40] has discovered that a significant percentage of patients previously categorized as idiopathic have autoantibodies to IgE [56] or the FcεRIα subunit of the high-affinity IgE mast cell receptor [57]. This represents the newly identified condition of autoimmune urticaria. Various studies have identified these autoantibodies in 24% to 76% of patients with chronic urticaria [58]. Clinically, these patients tend to have somewhat more severe, prolonged disease [59]. Middle-aged women disproportionately are represented in the population of patients with urticaria, and higher rates of autoimmunity in this group, particularly for thyroid disease, may account for this preponderance [60,61]. Thyroid autoantibodies are found more frequently in patients with these IgE-receptor autoantibodies [62].

Far less common than the physical urticaria or urticaria caused by autoantibodies is chronic urticaria caused by systemic disease. The list of condi-

tions reported to be associated with urticaria is enormous and beyond the scope of this article. The most significant of these conditions, however, belong to the categories of rheumatic conditions, other autoimmune conditions (including thyroiditis), infections, and neoplastic conditions. Although it is uncommon for urticaria to be associated with diseases of known or presumed immune complex deposition (eg, lupus, serum sickness, infectious viral hepatitis, cryoglobulinemia, rheumatoid arthritis), these lesions can occur and often are a leukocytoclastic vasculitis of the skin [28,35,63,64]. Urticarial vasculitis can occur as a unique entity and is discussed in detail by Davis and Brewer elsewhere in this issue [32]. An association between thyroid autoimmunity and chronic urticaria first was reported by Leznoff [65], and one large study of 624 patients found that 90 patients had evidence of antithyroid antibodies, whereas 37 patients might be expected to have these antibodies by chance alone [61]. Although urticaria can be seen as a manifestation of hypothyroidism (eg, Hashimoto's thyroiditis) or hyperthyroidism (eg, Graves' disease) [66,67], patients most commonly are clinically and biochemically euthyroid [61]. These associations between urticaria and thyroid abnormalities are discussed in greater detail by Rumbyrt and Schocket elsewhere in this issue [68].

Infections have long been associated with urticaria, and viral infections are believed to be a relatively common cause of acute urticaria. Chronic urticaria has been associated with chronic infections caused by parasites, such as strongyloidiasis, giardiasis, malaria, and amebiasis, in areas that are affected by these infestations [42,69]. Traveling in underdeveloped areas, using unpurified water while camping, and other such history may yield clues and warrant relevant laboratory testing (eg, eosinophil count, stool for ova and parasite examination). Not infrequently, however, these conditions simply may be coexistent [70]. Other chronic infections, including sinus infections, dental infections or abscesses, *Helicobacter pylori* gastric infection, cholecystitis, onychomycosis, and tinea pedis, have been considered as possible associations, although rigorous proof of these associations is lacking [1,71,72]. The natural history of chronic urticaria probably accounts for some percentage of coincidental spontaneous improvement after treatment of these conditions.

Urticaria has been reported as a paraneoplastic syndrome [73], but occult neoplasia is unlikely to be the cause of chronic urticaria. Obvious signs or symptoms of cancer usually are present in cases of urticaria associated with neoplasia. A review of 1155 cases of chronic urticaria revealed only 36 instances of malignancies, whereas 41 cases might be expected by chance alone [7]. The distinctive and rare condition known as Schnitzler's syndrome, characterized by nonpruritic urticaria with vasculitis and a monoclonal IgM gammopathy [74], also may occur. Primary mast cell disorders, although rare, account for a few cases of chronic urticaria. Urticaria pigmentosa rarely is confused with chronic urticaria from other causes, given the distinctive pigmented cutaneous lesions for which it is named [75]. Even less common is systemic mastocytosis, a highly symptomatic but rarely malignant hyperplastic

condition of mast cells. Total numbers of mast cells are increased, and elevations of the constitutively expressed α form of tryptase can be detected and quantitated in the serum. This condition almost always is accompanied by other symptoms, including prominent gastrointestinal symptoms, neuropsychiatric symptoms, and recurrent anaphylaxis [76]. Mast cell disorders, including urticaria pigmentosa and systemic mastocytosis, are reviewed in detail by Brockow elsewhere in this issue [77].

Substantial numbers of patients with chronic urticaria seem to have symptoms in the absence of specific physical triggers, allergens, coexistent disease, or evidence of autoimmunity and are categorized as idiopathic. In most series, this presentation represents a significant majority of these patients, but must remain a diagnosis of exclusion. It is sometimes difficult for patients (and some physicians) to accept this fact, which can prompt more extensive, invasive, and expensive searches for “the cause”. After thorough consideration of the aforementioned associated possible causes and after performing a careful and detailed history, physical examination, and a few selected screening tests (discussed in detail later), it is helpful to encourage patients to accept the intrinsic idiopathic nature of their condition and to focus on attempting to achieve reasonable symptomatic control with safe and effective treatments. These modalities include medications and efforts to minimize factors that exacerbate symptoms (for a specific patient). These factors often include stress or anxiety, hormonal fluctuations, use of aspirin and other NSAIDs, and cutaneous vasodilatation (such as alcohol, hot baths or showers, exercise, waterbeds). Psychosocial stress is a commonly reported trigger for worsening symptoms [13,14]. A plausible biochemical mechanism for this trigger may include increased release of cutaneous neuropeptides known to lower the threshold for mast cell degranulation [5].

The prognosis for chronic urticaria is relatively good, and a review of 554 patients with chronic idiopathic urticaria by Champion et al documented spontaneous resolution of a single continuous episode within 12 months in 50% of patients [14]. An additional 20% of patients generally experienced resolution within 5 years, but 10% to 20% of patients had symptoms lasting 20 years; these rates of resolution were significantly less in patients who had also symptoms of angioedema. These patients, described as idiopathic, may have included many who now could be classified as having autoimmune urticaria. Patients with autoantibodies tend to have worse disease, but this finding is not dramatic [59,78]. Physical urticarias tend to run a longer course [14,45,46,50]. Not uncommonly, however, patients who have had one idiopathic episode of chronic urticaria for months or years may experience a similar later recurrence. The authors suggest the use of the term “chronic urticaria-persistent” for patients with continuous episodes lasting more than 1 year and the term “chronic urticaria-recurrent” for patients with briefer episodes (weeks to months) but frequent recurrences over several years. Although the pathophysiologies of both conditions remain unknown (and may be similar or different), the authors believe that this distinction is useful in terms of typical prognosis and approach to therapy.

Clinical evaluation

Even cursory consideration of the aforementioned issues makes clear the value of performing a thorough history and physical examination when evaluating patients with chronic urticaria or angioedema. As mentioned earlier, it is crucial to identify all medications (including prescription, over-the-counter, oral, topical, conventional, and herbal) that are taken intermittently or regularly and which the patient is actually using. It is not uncommon to see patients who have been to numerous physicians and who are taking multiple medications for control of their urticaria, including substantial courses of systemic steroids, but who remain on medications commonly associated with causing or exacerbating urticarial symptoms. Of particular concern is the use of aspirin and other NSAIDs (including cyclooxygenase 2 [COX-2] selective agents) [79–81], ACE inhibitors, ACE-receptor blockers [82], and β -blockers (antihypertensives, eye drops for glaucoma) [83]. Occasionally, patients using opiate analgesics experience urticaria through direct mast cell–releasing properties of these agents. The authors also have seen patients with chronic urticaria who have continued long-term immunotherapy for aeroallergen sensitivity but have not attempted a trial of discontinuation of these chronic allergen injections. For patients with tattoos, any correlation between recent application or removal of tattoos should be discussed, as tattoo pigments have been associated with cutaneous allergy [84–86]. Questioning about any history of latex sensitivity or possible exposures may reveal a potential occult contact allergen [87–89].

The appropriate role of laboratory testing and studies in chronic urticaria remains controversial. Historically, physicians' and patients' desires to not miss something serious and to find the cause of symptoms, combined with anecdotal associations of chronic urticaria with a multitude of various conditions, have led to exhaustive testing in many patients. This search was almost invariably fruitless in identifying any unsuspected underlying systemic illness or other specific cause for these symptoms [16,72]. Expert reviews progressively have recommended performing fewer and fewer routine screening tests and studies over time [90]. One review of 29 large studies of laboratory testing in chronic urticaria, involving 6462 patients, demonstrated no relationship between numbers of identified diagnoses and numbers of performed tests [91]. Systemic diseases (which excluded physical urticarias, allergens, infections, or psychologic causes) were identified and believed to be related causally to the urticaria only in 1.6% of patients; these diseases included vasculitis (60 patients), thyroid disease (17), lupus (7), other rheumatic disease (16), hereditary angioedema (2), and hematologic or oncologic conditions (12) [91]. This finding applies only to tests obtained for no specific indication other than the urticaria itself; any abnormalities found through performing a careful and detailed history and thorough physical examination should be pursued vigorously.

The use of screening skin testing for food allergies in this setting also is controversial. Many patients with food-induced urticaria have diagnosed themselves without the help of a specialist. Skin testing for foods in the patient with chronic

urticaria is fraught with false-positive and false-negative results. In the absence of a specific history suggestive of a particular food allergy (history of exposure and time course of subsequent symptoms consistent with typical food allergy), such skin testing can be counterproductive, particularly in patients with dermatographism and so-called “twitchy mast cells” [13]. One author (D.A. Dibbern) limits food allergy testing to cases in which a particular food, or limited number of foods, clearly is implicated by a detailed history. Patients with a vague notion that their symptoms must be caused by an unknown or unsuspected food allergen are encouraged to clarify this notion with the use of a formal written food-and-symptom diary. If limited numbers and types of particular foods are identified, selected and directed testing may be done, but it seems more common that patients’ diffuse sense of an unknown but reproducible food trigger usually does not stand up to careful scrutiny. The author believes that screening panels of food allergy tests are rarely helpful in this situation. Alternately, some forms of elimination diet trials may be considered, but this approach is cumbersome and difficult for most patients. The other author (S.C. Dreskin) administers skin tests for foods in patients who are overly concerned about dietary issues, choosing a higher threshold for a positive test (greater than the size of the positive control) and counseling patients regarding the need to remove and reintroduce the suspect food on multiple occasions before removing it from the diet entirely. This author feels that an elimination diet with guided challenges of omitted foods can be useful for selected patients to help them rule out foods as the cause of their urticaria.

Although definitive consensus has not been reached, the authors’ general approach to clinical evaluation of urticaria is as follows: (1) Review previous health screens performed by the primary care provider and all available information from other physicians (previous specialist consultation, laboratory testing); (2) obtain only tests and studies specifically indicated and as directed by abnormal signs and symptoms found in the history and physical examination (apart from urticaria proper); (3) if symptoms are difficult to control with antihistamines or persist beyond 3 months, check a complete blood cell count with (manual) differential, erythrocyte sedimentation rate (ESR), and thyroid studies (thyroid-stimulating hormone, antithyroglobulin and antithyroid peroxisomal antibody titers); (4) if the symptoms are atypical, are suggestive of urticarial vasculitis, or persist or worsen beyond 1 year, obtain complement studies, perform hepatocellular enzyme tests, and consider an antinuclear antibody (ANA) titer and skin biopsy. This approach takes into account the facts that chronic urticaria, in the absence of other signs or symptoms, is unlikely to be associated with occult systemic disease, often easily is controlled with antihistamines, and often spontaneously resolves within about 6 months to 1 year. Most of the uncommon cases with a detectable but unsuspected underlying cause (infectious and parasitic conditions, rheumatic conditions, thyroid conditions, and hematologic conditions) should be identified readily with a white blood cell count, differential (eosinophil count), ESR, ANA titer, complement studies, thyroid function testing (including antithyroid autoantibodies), and hemoglobin and hematocrit, respectively.

Although not routinely indicated in every case of chronic urticaria, obtaining a skin biopsy specimen can provide useful information in managing difficult or persistent cases. The most common specific indication for this procedure is to rule out urticarial vasculitis when this condition is suspected clinically. The predominant type of cellular infiltrate also may suggest a corresponding management approach if antihistamines alone are inadequate for control. A predominance of neutrophils may suggest a trial of agents such as hydroxychloroquine, sulfasalazine, or dapsone [92], whereas patients with substantial numbers of eosinophils in their biopsy specimen may respond better to steroids [93].

Research laboratories can detect the presence of anti-Fc ϵ RI α autoantibodies, but these tests are not standardized, nor routinely or widely available [58]. Some urticaria specialists assess this clinically and indirectly through autologous serum skin testing, whereby the patient's serum is centrifuged and used for skin prick testing in this form of a semiquantitative functional assay for autoimmunity to IgE or IgE receptors bound to cutaneous mast cells [94]. This test is about 75% sensitive and 74% specific for the presence of these autoantibodies [59].

Pathophysiology and current research

Mast cells are the primary type of effector cell in chronic urticaria and angioedema [120]. Chronic urticaria is characterized by an inflammatory infiltrate consisting of CD4⁺ and CD8⁺ T lymphocytes, eosinophils, basophils, and neutrophils [95,96]. In a substantial number of patients, autoantibodies to Fc ϵ RI α are present. The net result of autoantibody activation of mast cells and influx of inflammatory cells is release or generation of multiple mediators, including histamine, prostaglandin D₂, leukotrienes C₄ and D₄, platelet-activating factor, anaphylotoxins (C3a, C4a, C5a), bradykinin, histamine-releasing factors, cytokines, and chemokines [37]. There is also evidence for increased production of cytokines, including interleukin 4 (IL-4), IL-5, and interferon γ [96].

Although much remains obscure regarding the exact pathophysiologic mechanisms underlying most cases of chronic urticaria, a substantial minority of chronic urticaria seems to have an autoimmune basis. Since the discovery of IgG anti-IgE antibodies [56,97] and the more common IgG anti-Fc ϵ RI α antibodies [57] in the sera of patients with chronic urticaria, the role of autoantibodies has been an increasingly active area of urticaria research. Although rates of detectable anti-IgE or anti-IgE receptor vary among the several published studies, the report by Tong et al [98] is relatively typical, in which approximately 50% of patients have functional anti-Fc ϵ -RI, and approximately 10% have anti-IgE.

In studies of human leukocyte antigens in patients with chronic urticaria, a particular major histocompatibility complex class II allele (DR4) was found with increased frequency, particularly in patients with evidence of an autoimmune basis for their urticaria [99].

Treatment

Although current therapeutic options are covered in detail by J. Sheikh elsewhere in this issue [100], a brief overview of treatment of urticaria and angioedema is given. H₁ antihistamines are the cornerstone of the therapeutic armamentarium [101]. Continuing research on the exact mechanism of H₁ antihistamines has revealed that the use of the term “receptor antagonist” may be a misnomer, because all present H₁ antihistamines probably function as inverse agonists, stabilizing the receptor in an inactive conformation [102]. This finding may account for the clinical observation that H₁ antihistamines work better when taken prophylactically and are distinctly less effective after histamine has been released and is bound to the receptor [5,30,103]. These agents are reasonably effective for many patients, and one meta-analysis of 29 large studies of chronic urticaria noted that improvement with antihistamines was seen in 44% to 91% of 3591 patients from seven studies [91].

Certain H₁ antihistamines have been proposed as preferred for particular subtypes of chronic urticaria, such as hydroxyzine for cholinergic urticaria [5,46] or cyproheptadine (Periactin) for cold-induced urticaria [48,104], based primarily on anecdotal evidence or expert preference [105]. Some investigators have advocated using multiple H₁ antihistamines, changing or rotating agents, or using these drugs at dosages much higher than Food and Drug Administration-approved labeling recommends [5,26,27,106–111]. One review of the safety and efficacy of fexofenadine (Allegra) in chronic idiopathic urticaria noted that, in two large trials, there was little if any additional symptomatic benefit from dosages greater than 60 mg twice daily (through 240 mg twice daily), although this medication was tolerated in larger doses among healthy subjects [112]. Instead of using megadoses of H₁ antihistamines, the authors have found more clinical improvement and fewer side effects with the use of adjunctive medications of different and complementary classes (detailed later), compared with using high-dose or multiple H₁ antihistamines alone.

Although most histamine receptors in the skin are of the H₁ subtype, approximately 15% are of the H₂ subtype. The addition of an H₂ antihistamine is a logical adjunct to H₁ antihistamine therapy [113]. This combination has been found to provide additional clinical benefit for urticaria [114,115], although H₂ antihistamines alone do not seem to be clinically useful [116]. Ranitidine (Zantac) may have advantages over cimetidine (Tagamet), including higher potency and a lack of interference with hepatic microsomal enzymes and androgen receptors [117]. The tricyclic antidepressant doxepin has potent H₁ and H₂ antihistamine activity, with an H₁ receptor affinity nearly 800 times that of diphenhydramine and an H₂ receptor affinity six times that of cimetidine; it also has antimuscarinic, antiserotonergic, and anti- α -adrenergic activity [118,119] and may be used at much smaller doses than those typically needed for antidepressant effects. Despite dosing at night, doxepin use is limited substantially by significant side effects of sedation, increased appetite, and resultant weight gain.

Clinicians who care for patients with urticaria realize that symptoms often persist despite the use of maximal doses of antihistamines. This finding is not surprising considering the number of vasoactive and pruritogenic mediators released by mast cells, of which histamine is only one [4,120,121]. Antileukotriene medications have been used off-label for chronic urticaria with some success [122]. Although there seem to be few published cases reporting use of zileuton (Zyflo), a 5-lipoxygenase inhibitor, two reports suggests that this agent was more effective than zafirlukast, a leukotriene receptor antagonist [123,124]. Lipoxygenase inhibitors may more completely prevent leukotriene effects, in comparison with receptor antagonists; however, since the leukotriene receptor antagonists, which have a more convenient dosing schedule and a safer side-effect profile, have become available, these have been preferred in trials for patients with refractory urticaria. Production of Zyflo for the US market has ceased.

The unpredictable effects of NSAIDs on urticaria and angioedema have been appreciated for many years [5]. Nonspecific COX inhibitors have been known to cause or worsen symptoms in specific patients [125], but some patients have improved [28]. Although much of the relevant pathophysiology remains obscure, this enigma may be explained partly by effects from blocking prostaglandin E₂, which is a down-regulator of leukotriene synthesis [126]. In two anecdotal reports, specific COX-2 inhibitors have been used to treat urticaria [127,128]. It may be theoretically important that an antileukotriene already be in use to prevent potential exacerbations, presumably to avoid driving mast cell arachidonic acid metabolism from the COX pathways (prostaglandin production) and toward the 5-lipoxygenase pathway, increasing leukotriene production and possibly increasing symptoms.

Especially severe symptoms may require the relatively brief use of systemic corticosteroids to achieve symptomatic control, particularly in the uncommon event of significant and potentially life-threatening symptoms of angioedema or anaphylaxis [113]. These medications have serious potential side effects and are not indicated routinely for a chronic and otherwise benign condition [27,117]. Another potential risk is that some patients with urticaria have a significant flare of symptoms after steroid tapering or withdrawal [92], which can lead to a seesawing between symptoms and steroid treatment and discontinuation, followed by another symptom flare that requires yet another round of steroid therapy. Getting patients out of this vicious cycle can be challenging and requires a close physician–patient therapeutic alliance and mutual agreement on appropriate therapeutic goals [5,108]. It seems that a few patients with chronic urticaria seem to be completely unresponsive to high-dose systemic steroid therapy. These patients may be steroid-resistant or may represent a distinct subset of patients with different pathophysiologic [129] mechanisms at work.

Some patients with refractory symptoms have been treated with a wide variety of other medications. In a double-blinded, placebo-controlled trial, cyclosporin A has been shown to have activity in patients with anti-FcεRI autoantibodies [130]. Other treatments have been reported in a case-report format or in small case series. Adrenergic agents have been used historically to treat urticaria, can be

useful in selected cases, and sometimes are overlooked [131,132]. Other agents include calcium-channel-blocker antihypertensives [133,134], hydroxychloroquine [63], dapsone [135], colchicine [136], methotrexate [137–139], sulfasalazine [140,141], intramuscular gold [142], capsaicin [129], impeded androgens [143,144], and warfarin [145]. In addition to cyclosporine A, use of other immunosuppressive agents, including tacrolimus [108], azathioprine, cyclophosphamide [146], mycophenolate mofetil [147], plasmapheresis [148], and intravenous immunoglobulin [149], has been reported. Enthusiasm for the use of some of these more potent immunosuppressive agents should be tempered by concerns of potentially significant side effects [110,139,150,151].

Proposals for new directions and future research

Because urticaria, and particularly chronic idiopathic urticaria, is a common and important clinical problem, further study of the pathogenesis and treatment of this condition is crucial. Given the limited efficacy of presently approved antihistamine treatments and the significant side effects of steroids and cyclosporine, there is a pressing need to evaluate other anecdotally supported urticaria treatments in randomized, controlled trials.

As an adjunct to standard pharmacotherapy, there is much popular interest in exploring complementary and alternative approaches to the treatment of illness in modern medicine. In many ways, chronic urticaria is an ideal condition for study in this regard. It is often a persistent condition, commonly has relatively poor response to conventional treatments, significantly impairs quality of life but is rarely life threatening, and usually is associated with psychosocial stress. It is not uncommon for patients with chronic urticaria to seek various forms of alternative medicine, including homeopathic, naturopathic, herbalist, or kinesiologist treatments (D.A. Dibbern, Jr, MD, S.C. Dreskin, MD, PhD, unpublished data, 2004). There are limited data in the published Western medical literature on the use and value of these other approaches, such as cupping [152] or acupuncture [153]. Approaches that emphasize relaxation, such as transcendental meditation, biofeedback, visualization therapy, and other similar techniques may be helpful [154]. Hypnosis has been reported to be useful in a variety of skin conditions, including urticaria [155,156]. Many dermatologic conditions may be associated with substantial psychosocial distress; psychiatric or psychologic interventions may be useful in appropriate cases [154].

More basic research is needed on mast cell biology, particularly with regard to understanding the pathophysiologic mechanisms involved in physical urticarias. Are these varied stimuli physically disruptive to the mast cell itself, or do they trigger degranulation through physical effects mediated by receptors, cellular gates or channels, second messengers, or other pathways? Better knowledge of these processes might yield insights into new treatments for these forms of urticaria that are relatively recalcitrant to current conventional therapies. Similarly, development of new therapeutic agents that inhibit other known mast cell

activators or products, such as substance P, platelet-activating factor, tryptase, bradykinin, kallikrein, and eosinophil chemotactic factor, [4,5,120,121,157], should be investigated for effects on treatment of urticarial and angioedematous disease.

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