Part II: Chronic Urticaria/Angioedema

The following Annotations are detailed explanations of the algorithm.

**ANNOTATION 1: Does patient exhibit skin lesions consistent with chronic urticaria and/or angioedema?**

Urticaria is characterized by pruritic, erythematous, blanching, circumscribed macular or raised lesions involving the superficial layers of skin. Urticarial lesions classically wax and wane and do not persist in a given location for more than 24 hours. Such lesions are defined as chronic if manifestations are persistent or recurring over 6 weeks in duration (Fig. 1b). Persistent symptoms may be daily or episodic (weekly, monthly, etc). Diurnal patterns are often reported but these are highly variable from patient to patient. It is not possible to predict the duration of chronic urticaria/angioedema. Spontaneous remissions often occur within 12 months but a substantial number of patients continue to have symptoms at least periodically for years. Conditions that can masquerade as urticaria include but are not limited to the following entities: erythema multiforme minor, non-specific maculopapular exanthems, and mast cell releasability syndromes such as urticaria pigmentosa, (see Commentary 1 of Acute Urticaria and Commentary 1 of Chronic Urticaria for details). Hypersensitivity vasculitis (ie., urticarial vasculitis) should also be excluded (see Annotations 4–6). The skin lesions of urticarial vasculitis present with an urticarial appearance, but differ in that they persist 24 hours or longer in the same area, and may be palpable and purpuric. Following resolution, these lesions may leave residual pigmented changes in the skin. Urticarial vasculitis may be limited to the skin or be part of a systemic disorder. On occasion, patients with pruritus alone are referred for urticaria evaluation (see Commentary 1 for...
Angioedema involves swelling of deep subcutaneous regions in the skin and/or mucous membranes, such as a finger, hand, lip, tongue etc. There are many conditions that can masquerade as angioedema that must be considered when evaluating this skin manifestation (see Commentaries 1 of Acute Urticaria and Commentary 1 of Chronic Urticaria for details).

ANNOTATION 2: Does patient have chronic angioedema without urticaria? Commonly, patients experience the coexistence of chronic urticaria and angioedema. However, some patients may present with chronic angioedema without urticaria. Patients with this manifestation fall into a separate category that may require diagnostic evaluations for unusual conditions (see Annotation 3). The evaluation should move to Annotation 4 if there is urticaria with angioedema.

ANNOTATION 3: Evaluation of chronic angioedema without urticaria A detailed history, and physical examination are suggested to rule out underlying causes. Of particular importance is the family history because of the possibility of hereditary angioedema. Etiologic triggers include medications (eg, ACE inhibitors) occupational exposure (eg, latex sensitivity); insect sting reactions; physical hypersensitivity disorders (eg., cold urticaria that can present with generalized or regional angioedema following cold exposure); exercise-induced angioedema with or without anaphylaxis; pressure-mediated sensitivity that can cause angioedema of the feet following walking or running and less often food hypersensitivity. The managing physician may require the expertise of an allergist/clinical immunologist to evaluate unusual causes of angioedema (see Annotation 8 for other etiologies).

A history of angioedema alone may suggest a rare disorder of C1 esterase inhibitor deficiency, which may be inherited as a autosomal dominant or acquired angioedema due to C1 esterase inhibitor deficiency may present as an acute episode of regional swelling following trauma (eg, dental manipulation of the oropharynx) or episodic abdominal pain which is thought to be secondary to angioedema involving the intestinal tract. Although C1 esterase inhibitor deficiency may present as an acute episode, detailed history may confirm the recurrent nature of these disorders. It is advised that screening C4 levels be obtained on all patients with chronic angioedema without urticaria, especially patients with the aforementioned history. C4 levels are usually decreased during both symptomatic and asymptomatic periods of the disease, while C2 levels are reduced only during attacks. If the C4 level is reduced, quantitative C1 esterase inhibitor levels should be obtained. If these levels are normal, a functional assay should then be done. Fifteen percent (15%) of patients with hereditary C1 esterase inhibitor deficiency have evidence of dysfunctional inhibitor protein with normal quantitative levels of C1 esterase inhibitor.

Patients with chronic angioedema without urticaria may have acquired C1 esterase inhibitor deficiency associated with a lymphoproliferative disorder or a systemic connective tissue disease. A reduced C1q in association with decreased C1 esterase inhibitor and C4 warrants evaluation for an occult lymphoproliferative disorder. The presence of C1q autoantibody and/or C1 esterase inhibitor autoantibody suggests an underlying connective tissue disease although it may be present without evidence of an underlying disease. C1q autoantibody is sometimes associated with lupus erythematosus.

ANNOTATION 3b: Specific management of an underlying cause of chronic angioedema without urticaria Individuals with recurrent angioedema that is a manifestation of anaphylaxis should carry an emergency epinephrine kit (eg, EpiPen). In addition, specific management should be instituted once an etiology of angioedema without urticaria has been established. Latex-induced angioedema would require elimination of latex exposure and possible removal of cross-reacting food allergens from the patient’s diet (eg, banana, avocado, grapes, peaches, apricots, cherry, pineapple, kiwi, chestnut, etc). Recurring urticaria/angioedema due to cold sensitivity requires avoidance of cold exposure, particularly immersion (eg, aquatic activities) and possible prophylaxis with cyproheptadine, second generation antihistamines or doxepin.
The treatment choices for recurrent acute life threatening attacks of C1 esterase inhibitor deficiency (hereditary or acquired) are limited and usually supportive. Some clinicians advocate treatment with plasma infusions or C1 esterase inhibitor concentrates although the latter are not commercially available.37,38 Should these measures fail, intubation or tracheostomy may be necessary. For frequent episodes of angioedema due to C1 esterase deficiency, prophylactic management is possible with anabolic steroids (eg, Danazol or Stanazolol). Because of the danger of trauma-induced exacerbations, short-term prophylactic anabolic steroids 4 to 5 days prior to elective dental or surgical procedures should be considered.39 Annotations 10, 13, 14 discuss nonspecific considerations for treatment of angioedema with or without urticaria.

ANNOTATION 4: Do patients with chronic urticaria (with or without angioedema) exhibit lesions suggestive of urticarial vasculitis? Although the prevalence of urticarial vasculitis is low, it is nevertheless important to recognize because this disease can be associated with other systemic conditions (ie, the Henoch-Schönlein syndrome) and is amenable to effective treatment. If skin lesions have an urticarial appearance and last longer than 24 hours in the same location, urticarial vasculitis (ie, hypersensitivity vasculitis) should be considered.4,6–9 Typically these urticarial-like lesions: (1) are less pruritic and more painful than observed with true chronic urticaria, (2) are more prominent on lower extremities, (3) may be palpable and purpuric, and (4) following resolution may leave pigmented changes in the skin. Angioedema may accompany urticarial vasculitis.40 In addition, urticarial vasculitis may be associated with systemic symptoms such as low-grade fever, arthralgia/arthritis, gastrointestinal complaints, pulmonary and ocular symptoms.4,6–9,41 Urticarial vasculitis is thought to be due to immune complex mediated inflammation (see Commentary 2 for details on mechanisms). The evaluation should move to Annotation 8 if urticarial lesions remain less than 24 hours in the same location.

Occasionally, history and examination may not provide definitive evidence of urticarial vasculitis. If urticarial vasculitis is suspected, it may be necessary to evaluate specific lesions at 24 hours, 36 hours, and 48 hours after the initial evaluation. Specific lesions should be circled and numbered as part of the ongoing assessment. Lesions that remain fixed beyond 24 hours require further diagnostic evaluation for urticarial vasculitis (see Annotation 5).

ANNOTATION 5: Evaluation of suspected urticarial vasculitis If urticarial vasculitis is suspected, a punch biopsy of a suspected skin lesion should be obtained. Urticarial vasculitis lesions reveal a specific histopathology described in Annotation 6. Immunofluorescence of the skin biopsy may determine the presence of fibrinogen, immunoglobulin (eg, IgA, IgG, and IgM) and/or complement deposition, several or all of which are indicative of immune complex mediated events.6–9 Other tests that may be useful include complement assays to rule out complement depletion (eg, CH50, C3, Factor B, and C1q)7,8 and cryoglobulins. Immune complex assays (Raji assay and C1q binding) have limited sensitivity and specificity.8,42 The erythrocyte sedimentation rate and/or C-reactive protein may be elevated in urticarial vasculitis.

ANNOTATION 6: Does patient have urticarial vasculitis? The diagnosis of urticarial vasculitis is confirmed by the histopathologic results of the skin biopsy.6,43 This includes polymorphonuclear infiltration within the walls of blood vessels and in the perivascular space. Leukocytoclasia (ie, fragmentation of neutrophils) is frequently noted along with endothelial swelling, red blood cell extravasation and fibrin deposition. Complement levels (eg, CH50) may be normal or decreased in this condition. Hypocomplementemia associated with urticarial vasculitis has a worse prognosis and is suggestive of systemic disease.6 A decreased C1q level may be a sensitive marker of complement activation in patients with urticarial vasculitis. If there are decreased complement indices and/or C1q levels, a more thorough evaluation for systemic disease involving the renal, gastrointestinal, pulmonary, ocular, and musculoskeletal systems should be considered.43 Other serious diseases should be considered in the differential diagnosis of vasculitis6–9,43 (see Commentary 2).

ANNOTATION 7: Management of urticarial vasculitis Patients with urticarial vasculitis should be managed by physicians with expertise in these conditions. Antihistamines may be useful in managing the pruritus associated with urticarial vasculitis9 (see Annotation 14). Other symptoms due to immune complex mediated inflammation may not respond to antihistamine therapy. Patients with moderate or severe cutaneous disease, especially those with systemic manifestations, may require treatment with anti-inflammatory agents, such as: glucocorticosteroids, indomethacin, colchicine, dapsone and hydroxychloroquine.6 Cytotoxic agents (eg, methotrexate,44 azathioprine,45 cyclosphosphamide) can be used cautiously to reduce the dose requirements of corticosteroids. Patients receiving these medications require careful monitoring for potentially serious side effects associated with use of these agents.

Patients with urticarial vasculitis should be monitored for evidence of systemic disease that might affect the renal, gastrointestinal, pulmonary, ocular, and musculoskeletal systems. For example, periodic urinalysis and creatinine clearance (if indicated) should be performed to rule out renal involvement. Referral to a nephrologist may be indicated if significant and progressive renal abnormalities are detected. Annual ophthalmological referrals may also be appropriate.
system symptoms involving joints, gastrointestinal tract, pulmonary, renal or ocular systems could suggest a systemic disease associated with urticaria/angioedema (eg, vasculitis, collagen vascular disease). A complete physical examination may provide unsuspected clues to the etiology of chronic urticaria/angioedema. The physical evaluation should include all systems to rule out serious underlying diseases (eg, malignancies, mixed connective tissue diseases, chronic hepatitis, chronic infections, cutaneous or systemic mastocytosis, cryoglobulinemia, etc). Association with other skin lesions may be helpful in the differential diagnosis of chronic urticaria; thus, residual discoloration of fading urticaria especially on the legs suggests urticarial vasculitis. Concomitant bullous eruptions would suggest cutaneous blistering conditions such as bullous pemphigoid or dermatitis herpetiformis. Reddish tan pigmented macules that urticate on stroking would suggest urticaria pigmentosa. Palpable purpura on lower extremities is seen with cryoglobulinemias or leukocytoclastic vasculitis. Specific physical findings in the skin or other systems may direct the diagnostic evaluation.

Laboratory test confirmation is essential if an etiology is suspected by history and/or physical examination. If they have not already been obtained, basic laboratory tests are advised as a screening approach for underlying diseases. The panel might include a CBC, ESR, urinalysis and liver function tests. Because thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) and anti-FcεI receptor antibodies are being reported with increasing frequency, some clinicians recommend that these tests be obtained if the initial screening panel is noncontributory and the urticaria/angioedema persists.\(^5,59-61\) Other tests could be added to the screening panel based on clinical indications. Specific laboratory tests should be selective and based only on diagnostic suspicions (see Commentary 3 for more testing details). If, at the initial presentation, chronicity of the patient’s symptoms is already established in terms of months or years, it is justified to proceed directly to the next level of evaluation described in Algorithm Box 11 and Annotation 11. Under these conditions, evaluation of possible autoantibodies (eg, thyroid, anti-high affinity, FcεI receptor), as described above, and/or histopathologic data could be useful adjuncts in deciding optimal management (see Algorithm Box 10 and Annotation 10). Commentary 3 also provides additional information about other possible helpful diagnostic pathways to detect triggers of mast cell activation at this stage of the patient’s evaluation.

ANNOTATION 9: Is the evaluation of chronic urticaria (with or without angioedema) indicative of an underlying cause?

An underlying cause may be determined after data have been accumulated and are consistent with the history, physical examination and laboratory tests. Refer to Commentary 3 for other causal relationships suggested by history, physical examination and confirmatory laboratory tests.

ANNOTATION 10: Specific management of chronic urticaria (with or without angioedema)

The management of urticaria/angioedema will, in part, be dictated by the etiology. For example, avoidance of offending antigens when identified (eg, drugs, foods, venom from insect stings, latex, etc)\(^1-5,11,13\) applies to generalized and localized contact urticaria caused by antigen-induced IgE mechanisms. Non-specific agents that are known to exacerbate urticaria/angioedema (aspirin, NSAIDS, opioids, alcohol) and that could stimulate mast cells should be avoided. Several physical hypersensitivity syndromes respond to specific therapeutic regimens. Idiopathic (ie, primary) acquired cold urticaria responds to prophylactic treatment with a variety of first generation antihistamines (in particular, cypohedrine and hydroxyine), second
generation antihistamines (loratadine, fexofenadine, and cetirizine) and tricyclic antidepressants (doxepin). Cho-
linergic urticaria can be treated with various antihistamines.64,65 Delayed pressure urticaria is treated with first and second generation antihistamines and may require courses of oral glu-
corticosteroids (eg, daily or if possible, every other day treatment) or other regimens including dapsone, NSAIDS, and sulfasalazine.58,66,67 Selected cases of exercise-induced urticaria with or without anaphylaxis may require pro-
phylactic treatment with first and/or second generation antihistamines which may help to reduce the fre-
quency and/or intensity of attacks.66,67 A prescription for an emergency epi-
nephrine kit (eg, Epipen) is advised for individuals with a concomitant history of anaphylaxis or laryngeal angio-
edema. In addition, occult food or drug allergies in combination with exercise may induce symptoms.69–71 In such
cases, it is advised that patients avoid food or drug ingestion several hours before and after exercise. Dermatogra-
phism is best managed by patient awareness not only concerning the relation-
ship of hives to scratching but also the need for prophylactic treat-
ment with antihistamines.72 It may be necessary to treat a suspected infectious disease associated with urticaria and/or angioedema, such as hepatitis C, with alpha interferon and/or ribaviri-
rin.73 Treatment of an autoimmune dis-
order associated with urticaria/angio-
edema is dictated by the specific autoimmune disease. For example, treatment of autoimmune thyroid dis-
orders with thyroid hormone may be associated with improvement or remis-
ion of urticaria.59–61 Therapy of urti-
caria/angioedema occurring with other
generalized diseases is dictated by the spec-
ific underlying condition (eg, neo-
plasms, systemic vasculitis, collagen vascular disorders, etc).

In addition to specific treatment of an underlying condition, management should be oriented towards palliation of symptoms. In general, removal of potential urticarial aggravants such as aspirin, NSAIDS, or alcohol is advised regardless of the underlying etiology. For most patients, symptomatic treat-
ment with H1 antihistamines remains the mainstay of management.74,75 Sedation from first generation antihis-
tamines may be desirable for reducing the discomfort of pruritus associated with urticaria. First generation antihis-
tamines, however, may cause undesir-
able and potentially dangerous side ef-
effects including driving impairment and risk for fatal automobile accidents.66,77 decreased workplace productivity,78 in-
creased risk for occupational accidents, increased risk for falls in nursing home patients, and in children, impaired learn-
ing and academic performance.79 Impor-
tantly, studies have demonstrated that many patients may not perceive perform-
ance impairment from first generation antihistamines, and that there is no cor-
relation between subjective perception of sedation and objective performance impairment.80 In contrast, second gener-
ation antihistamines (loratadine, fexofe-
nadine, and cetirizine) at recommended doses are associated with minimal risk for these adverse effects, although cetiri-
zine may have mild sedative effects. Accord-
ingly, the decision to choose be-
tween first and second generation anti-
histamines for treatment of urticaria should consider these differences.

Both first and second generation an-
thistamines also exhibit anti-allergic and anti-inflammatory effects but such properties do not consistently contrib-
ute to the overall clinical responses induced by this class of drugs.75,81,82 Combinations of various antihista-
mines and alternative therapeutic regi-
mens such as glucocorticosteroids, other anti-inflammatory agents, $\beta_2$
agonists, calcium channel blockers and anti-leukotriene drugs are discussed in
Annotation 14.

**ANNOTATION 11: Further evaluation of chronic urticaria (with or without angioedema)**
A more detailed review of the history, review of systems, and physical exam-
ination may be warranted to uncover a previously unrecognized underlying condition associated with urticaria/angioedema. The discovery process may in part require the physician’s careful observation of the urticaria/angio-
edema process over a protracted period of time. New observations may emerge that can provide clues to an underlying diagnosis. Teaching the patient to be-
come more observant may be helpful and has been widely recommended. For example, prolonged use of detailed diaries has been used in an attempt to identify triggers and give a sense of participation in care. This process rarely detects a cause and may lead the patient to develop an unhealthy obsession with his/her urticaria. On the other hand, patient participation can be ac-
complished by reinforcing the patient’s adherence to treatment recommenda-
tion in the hope that the hives will spontaneously resolve. The long-term management of refractory chronic ur-
ticaria/angioedema is greatly facili-
tated when there is good rapport be-
tween physician and patient because continuous reassurance is required.

New observations may dictate more detailed review of systems, physical examina-
tion and specialized laboratory evaluation. For example, a patient may develop symptoms of hypothyroidism in association with chronic urticaria. A careful examination of the thyroid would then be advised along with tests to evaluate thyroid function and pres-
ence of autoimmune thyroid disorders (ie, anti-thyroid peroxidase/anti-thyro-
globulin antibodies and autoimmune panels).59–61 Since one or both thyroid autoantibodies may be present in up to 28% of patients with chronic urticaria/angioedema, some clinicians advocate that these tests be obtained, especially in women or in those patients with a family history of thyroid or other au-
toimmune disease.83 In other sit-
uations, the managing physician might consider other tests depending on as-
sessment of new or additional information. For example, hematologic leuke-
mic markers might be ordered in a patient with acquired cold urticaria with cryoglobulinemia in order to rule out an underlying chronic lymphocytic leukemia process.84 Imaging proce-
dures may be helpful at this juncture, depending on the need to evaluate a
specific anatomical region in more detail. As part of the on-going re-evaluation, repeat or more detailed multi-system screening blood test panels may be indicated.

Other areas of evaluation may include trial elimination diets initially and/or limited food specific IgE tests (ie, percutaneous skin tests; in vitro tests) if foods are implicated by history or diary data as potential causes of the symptoms. In this situation, prick/ puncture tests are preferable, provided dermatographism is not present. Positive food specific IgE tests would in turn suggest further confirmatory food elimination trials. Open-single or double-blinded placebo-controlled food, food additive, or drug challenges may also be useful. These challenge procedures require close monitoring for symptoms of anaphylaxis.

A skin test with autologous serum may reveal a wheal and erythema response suggesting the presence of anti-IgE or anti high affinity IgE receptor antibodies.

A body of clinical evidence is emerging that recommends a punch skin biopsy be performed on patients with difficult to treat chronic idiopathic urticaria. Two groups of chronic urticaria have been defined by skin biopsy results: (1) perivascular lymphocyte-predominant urticaria and (2) perivascular polymorphonuclear—predominant urticaria (ie, neutrophils, scattered eosinophils and mononuclear cells). Several interesting clinical observations have been associated with each group. Patients with lymphocyte-predominant infiltrates are more responsive to antihistamine therapy. Patients with polymorphonuclear cell-predominant infiltrates are relatively resistant to antihistamines and will more likely require oral glucocorticosteroid treatment. In addition, patients having IgG anti-IgE or IgE receptor autoantibodies often exhibit evidence of perivascular polymorphonuclear cell-predominant infiltrates in skin biopsies. Eosinophil activation may occur later or be more persistent in patients without autoantibodies. The skin biopsy may also detect unsuspected urticarial vasculitis or mastocytosis. The latter requires metachromatic stains such as Giemsa or toluidine blue for detection of increased numbers of mast cells (usually >4 per high power field).

ANNOTATION 12: Is additional evaluation of chronic urticaria (with or without angioedema) indicative of an etiology?

An underlying cause may be determined after data has been accumulated and analyzed from the history, physical examination, and laboratory tests. For example a skin biopsy might reveal unsuspected urticaria pigmentosa with evidence of mast cell aggregates revealed by metachromatic stains. Other examples might be evidence of symptom induction during open-single or double-blinded placebo-controlled food, food additive or drug challenges. At this juncture, the managing physician decides whether an underlying etiology has been established. Refer to Commentary 3 for other causal relationships suggested by history, physical examination and confirmatory laboratory tests.

ANNOTATION 13: Management of specific etiology of chronic urticaria (with or without angioedema)

The management of urticaria/angioedema will, in part, be dictated by the specific etiology. For example, if a skin biopsy reveals either urticaria pigmentosa or mastocytosis, treatment would be tailored to this diagnosis and should include avoidance of trigger factors (eg, friction) and non-specific mast cell releasing agents (eg, alcohol, aspirin, opiates etc). Specific pharmacologic therapy might include combinations of antihistamines, cautious use of cyclooxygenase inhibitors, pre-chemotherapy with oral 8-methylpsoralen (ie, PUVA), and/or oral disodium cromoglycate for bullous mastocytosis and gastrointestinal manifestations of systemic mastocytosis. Another example would be identification of a food as a possible cause demonstrated by an open single-blinded food challenge or a double-blinded placebo-controlled challenge. The managing physician would eliminate the putative food from the patient’s diet. It is important to recognize that isolation of a food substance as a cause of chronic urticaria/angioedema is rare. Refer to Annotation 10 for more examples of specific management strategies dictated by diagnosis of an underlying disorder. In addition to specific treatment of an underlying condition, management should be oriented towards palliation of symptoms which is also described in Annotation 10. For most patients, symptomatic treatment with antihistamines is advised and described in Annotation 10. If indicated, the use of glucocorticosteroids and other anti-inflammatory agents is outlined in Annotation 14.

ANNOTATION 14: Treatment of chronic idiopathic urticaria (with or without angioedema)

At this stage of the evaluation it is reasonable to define chronic urticaria/angioedema as idiopathic since this is a diagnosis by exclusion of underlying etiologies. If treatment is ineffective up to this point, referral to an allergist/clinical immunologist or dermatologist might be considered. The therapeutic management should first be oriented towards palliation of symptoms which is discussed in Annotation 10.

Combinations of various antihistamines may be useful in suppressing symptomatology. These include (1) first generation H1 antihistamines, (2) combinations of first and second generations using non-sedating agents in the morning and first generation drugs at night, (3) combinations of second generation antihistamines, (4) combination of an agent with both H1 and H2 anti-receptor activity (ie, doxepin) with a first or second generation antihistamine, and (5) combination of an H2 anti-receptor antihistamine [eg, cimetidine (Tagamet) or ranitidine (Zantac)] with a first or second generation antihistamine. Managing physicians should acquaint themselves with the side effects, as discussed in Annotation 10, and drug-drug interactions.
when using any combination of pharmacological agents.

Antihistamines may not be entirely effective in controlling urticaria because other capillary permeability inducing mediators are released (eg, leukotrienes; prostaglandin D2; kinins; platelet activating factor, etc). Glucocorticosteroid treatment may be appropriate when antihistamines are not effective. These agents are helpful in controlling the inflammatory cell influx that can potentiate the urticaria by secondary release of histamine releasing factors and cytokines. Managing physicians should explain the potential side effects associated with glucocorticosteroids. In some clinical situations, the managing physician or patient may request more evidence to justify the initiation of glucocorticosteroid therapy. A skin biopsy with perivascular predominant-polymorphonuclear cell urticaria may justify initiation and continuation of glucocorticosteroid treatment. As soon as possible, glucocorticosteroid therapy should be discontinued or reduced to minimal requirements such as an every other day regimen to reduce potential side effects. On rare occasions, chronic urticaria/angioedema may not respond to antihistamines. Preliminary reports suggest antihistamines may become life threatening or present as manifestations of anaphylaxis. Patients may present with other symptoms of anaphylaxis that may require emergency treatment, as discussed in Annotation 5 of Acute Urticaria. The mainstay of treatment for this emergency is epinephrine in doses dependent on the patient’s age. Intramuscular administration of epinephrine in children has been shown to produce a faster time of action than subcutaneous administration. Other treatment modalities include parenteral H1 and/or H2 antihistamine antagonists and parenteral glucocorticosteroids. Close monitoring of vital signs and oxygen measurements (eg, pulse oximetry; arterial blood gases) may be necessary, as rarely a patient (eg, hereditary or acquired C1 esterase inhibitor deficiency) may require intubation to overcome a compromised airway.

The following Commentaries (1, 2, and 3) provide further details and references

COMMENTARY 1: Differential diagnosis of chronic urticaria, angioedema and pruritus

Erythema multiforme minor is often preceded by prodromal symptoms of malaise, fever, sore throat, muscle aches, arthralgia followed by pleomorphic cutaneous responses (ie, macular, papular, frequently iris or target-like lesions, and rarely urticaria). More importantly, the lesions of erythema multiforme minor do not wax and wane; rather they remain fixed, are more frequently acral in distribution and usually burn or sting in contrast to urticarial lesions which are pruritic. Papular eruptions secondary to insect bites tend to occur on lower extremities and/or other exposed areas and persist longer than urticaria. Urticaria pigmentosa should be considered in the differential diagnosis of chronic urticaria if linear bead-like urticaria is induced by stroking over pigmented macular lesions (Darier’s sign).

Pruritic disorders can be erroneously assumed to be caused by urticaria. Chronic pruritus can be associated with systemic diseases involving the renal, hepatic and/or thyroid systems, diabetes mellitus, polycythemia vera, lymphoproliferative disorders, neoplasms, xerosis, pregnancy, and psychiatric disorders.

Conditions masquerading as angioedema are varied and physicians handling angioedema must be aware of the following systemic disorders: fluid overload, trauma, systemic capillary permeability syndrome, venous obstruction (eg, facial edema caused by superior venal caval syndrome), contact dermatitis, serum sickness, parotid gland obstruction, infection, myxedema, chronic inflammatory disease of autoimmune origin such as dermatomyositis, malignancies, lymphedema, chronic granulomatosis and/or infiltrative diseases such as sarcoidosis, amyloidosis and granulomatous angioedema involving the lips and perioral regions (ie, Melkersson-Rosenthal syndrome). Psychogenic pseudo-angioedema should also be considered in the differential diagnosis.

Angioedema and/or urticaria can be early warning manifestations of anaphylactic reactions. The occurrence of anaphylaxis can be established retrospectively if serum beta-tryptase levels are elevated. This blood test should be obtained within 2 hours of the onset of anaphylactic symptoms although elevated tryptase levels may persist for 4 hours or longer after the appearance of symptoms. Elevation of alpha-tryptase (by subtracting beta-tryptase from total tryptase) is indicative of diffuse cutaneous or systemic mastocytosis.
COMMENTARY 2: Immunopathology of urticarial vasculitis and underlying disease states associated with urticarial vasculitis

Urticarial vasculitis is thought to be due to immune complex mediated inflammation.\(^4,6\) Complement is activated leading to anaphylatoxin (C3a, C5a) production. Anaphylatoxins bind to mast cell receptors causing mast cell degranulation and vasoactive mediator release. Urticaria/angioedema results from the increased capillary permeability effects of released vasoactive mediators. Neutrophil infiltration results in part from immune complex induction of neutrophil chemotactic factors (C5a).\(^6\)

Urticarial vasculitis may be associated with disorders such as connective tissue diseases\(^1,12\) (eg, rheumatoid arthritis, lupus erythematosus, and Sjögren’s syndrome); serum sickness; infectious diseases such as chronic viral hepatitis (A, B, and C); Lyme disease; myelomas, cryoglobulinemias and Schnitzler’s syndrome (bone pain, fever, fatigue, weight loss, leukocytosis, anemia, elevated sedimentation rate, and IgM cryoglobulinemia). Medication-induced vasculitis (eg, the Churg-Strauss syndrome) should also be considered in the differential diagnosis of this condition.

COMMENTARY 3: Detailed history and laboratory testing for evaluation of chronic urticaria (with or without angioedema)

A. History

A history is essential for determining the etiology of chronic urticaria/angioedema. It should include questions related to specific etiologic considerations.

A thorough drug history\(^1\) should be elicited and include medications administered at least 1 month prior to and up to onset of symptoms. For example, penicillin administered 2 to 4 weeks prior to onset of symptoms can be responsible for serum sickness presenting with urticaria.\(^1,16\) ACE inhibitors,\(^12\) aspirin, other NSAIDS\(^63\) can exacerbate and/or cause chronic urticaria and/or angioedema.

A food diary and history of temporal relationship of symptoms to food ingestion may occasionally elicit an unsuspected food or food additives as a cause of chronic urticaria/angioedema.\(^85,86\) but this is a rare finding.

Chronic urticaria and/or angioedema may be associated with physical hypersensitivity disorders\(^48\) such as cold-induced urticaria\(^46\) and/or angioedema, which is one of the most common physical urticaria disorders; delayed pressure-induced urticaria; dermatographism; vibratory-induced urticaria/angioedema\(^46\); localized heat-induced urticaria; cholinergic urticaria\(^48\) (characterized by fine papular urticaria associated with exercise or passive body warming that does not progress to anaphylaxis); aquagenic-induced urticaria\(^15\); solar-induced urticaria\(^45\); and exercise-induced anaphylaxis which is often associated with giant urticaria, angioedema, respiratory distress, gastrointestinal symptoms, hypotension and syncope.\(^71\) If this entity is suspected, a detailed food and drug history\(^69\) is advised to rule out food or drug as a co-factor. Apart from delayed pressure urticaria, the physical urticarias are pathogenetically unrelated to chronic urticaria because they usually last less than 2 hours and they do not demonstrate either lymphocytic or polymorphonuclear perivascular cellular infiltrates.

The history should determine the presence of underlying infections. Chronic infectious illness as an etiology of chronic urticaria and/or angioedema is very controversial and is primarily based on anecdotal evidence of single case reports. However, there is evidence to suggest an association between chronic viral infections such as hepatitis (A, B, and C) and serum sickness and/or urticarial vasculitis. In addition, other viral diseases can be associated with chronic urticaria induction (eg, acquired cold urticaria with infectious mononucleosis).\(^118,119\) There are anecdotal reports associating chronic bacterial infections (eg, sinus, wounds etc) as causes of urticaria/angioedema, possibly via bacterial activation of complement.\(^90\) Other infectious illness that has been associated with chronic urticaria/angioedema include chronic fungal infections, especially tinea pedis,\(^120\) and chronic parasitic infestations.\(^41\) However, an extensive workup for occult bacterial and/or fungal infections is not justified.

The history should consider the possibility of an autoimmune etiology. Autoimmune disorders are occasionally associated with chronic urticaria and/or angioedema. Examples include: autoimmune-induced thyroiditis associated with anti-thyroid peroxidase antibodies\(^59–61\), systemic lupus erythematosus; and mixed connective tissue disorders. Autoimmunity may underlie chronic idiopathic urticaria.\(^52,53,87\) There is evidence of IgG anti-IgE autoantibodies and also IgG autoantibodies to the high affinity IgE receptor on the mast cell (ie, IgG anti-FceRI). This mechanism may explain the persistence of chronic urticaria/angioedema despite the absence of a specific exogenous sensitizing antigen.

The history should consider hormonal dysfunction. Hormone-induced disorders associated with chronic urticaria/angioedema include urticaria associated with pregnancy [ie, pruritic urticarial papules and plaques of pregnancy (PUPP)\(^121\), urticaria associated with menstrual hormonal changes,\(^53–55\) and autoimmune thyroid disorders with evidence of antithyroid autoantibodies.\(^59–61\)

The history may suggest the presence of an underlying malignancy. The association of malignancy, particularly lymphoreticular, and chronic urticaria/angioedema is based primarily on individual case reports.\(^49\) Pruritus without urticaria may also be associated with malignancy.

Occupational history is necessary to rule out work exposure to sensitizing antigens such as latex,\(^13\) as well as antibiotics, or chemicals in health, pharmacy or other occupations. Latex sensitivity may also develop after various types of nonoccupational exposure.
A history of exposure to insect stings/bites is essential. Particular attention should focus on the type of insect (eg, vespid14,15, honey bee14,15, fire ant122), and the physical consequences of the sting/bite. Rarely, late onset reactions to insect venoms may involve immune complexes manifested by angioedema, nephropathy and/or central nervous system signs.123,124

The history should elicit the presence of contact-induced urticaria. Contact-induced urticaria may be caused by latex exposure in gloves13; handling foods such as nuts, fish, or shellfish; direct handling or contact with sensitizing chemicals such as penicillin,125 formaldehyde126 in clothing; and by animals licking salivary proteins onto skin. In most cases contact urticaria is acute although patients exposed to contact allergens on a recurrent basis may present with a chronic history.

A family history should be elicited to rule out genetic forms of urticaria/angioedema such as Muckle Wells syndrome127 (urticaria, deafness, amyloidosis); delayed cold-induced urticaria16 and hereditary angioedema (see Annotation 3).

The history should rule out psychological factors that could aggravate chronic urticaria/angioedema98. Depressed or anxious individuals and elderly individuals with dementia may chronically irritate xerotic, dermatographic skin, causing repeated outbreaks of urticarial-like lesions.

The history may suggest a metabolic cause for chronic urticaria. For example, there are several well-documented case reports describing the temporal eradication of chronic urticaria following parathyroidectomy for primary hyperparathyroidism.128,129

B. Laboratory

Laboratory tests for chronic urticaria/angioedema should be selective depending on specific historical considerations. Although it has been proposed that a highly sensitive penicillin-allergic patient could develop urticaria/angioedema after unsuspected exposure to penicillin in cow’s milk, the current clinical evidence for this is unimpressive.130–132 Depending on clinical circumstances, the workup might include skin testing to both the minor (minor determinant mixture or penicillin G) and major determinant of penicillin (Pre-Pen) and/or complement tests (eg, CH50; Clq binding or Raji immune complex assay; cryoglobulins)41 to determine presence of immune complex-mediated serum sickness. Drug skin testing by skin prick/puncture or intracutaneous methods should be performed by physicians with expertise in interpretation of the results who have experience in handling adverse reactions (ie, anaphylaxis). On occasion, drug challenges may be necessary to clarify a causal relationship with a suspect drug. Oral drug challenges should be performed by physicians with experience in this procedure (eg, allergist/clinical immunologist) using an open challenge or placebo-double blind format.

As emphasized previously, it is extremely rare to demonstrate a causal relationship between chronic urticaria/angioedema and the detection of specific IgE antibodies to food antigens either by skin tests or in-vitro tests.55,66 Thus, except under rare circumstances, skin testing or in vitro tests for food-specific IgE antibodies are not indicated, and if done, should be selective based on historical correlation. Other in vitro tests (eg, food-specific IgG or IgG 4 antibody tests) are not reliable for evaluation of this condition.133 Further, food elimination diets are generally not helpful in alleviating chronic urticaria/angioedema. Food challenges may be useful in eliminating concerns about food/additive induction of chronic urticaria/angioedema. Food challenges should be performed by physicians with experience in this procedure, using open challenge or a placebo-controlled single or double-blind format.

Laboratory testing for physical hypersensitivity disorders depends on the suspected disorder.16,48 Cold testing for cold urticaria requires application of a cold stimulus (eg, ice cubes in a plastic bag) to the forearm. Wheal induction occurs after the cold stimulus is removed and the skin re-warms. Unfortunately direct cold application may be negative in atypical forms of cold urticaria. A history of light pressure sensitivity may require scratching the skin surface to induce dermographism. Deep pressure urticaria is verified by application of a weight strapped to the shoulder or thigh of a patient with this condition (eg, 15 lb in weight for 15 minutes).48 Deep swelling will often appear 2 to 12 hours after application of the weight. Application of a vibratory stimulus to the skin can be used to elicit vibratory urticaria. Exercise testing under monitored conditions may be necessary to rule out exercise-induced urticaria/anaphylaxis and cholinergic urticaria, which produces classic pustate urticaria. Other physical factors that may induce urticaria (eg, heat, solar, and aquagenic stimuli) require specific clinical diagnostic tests.

The likelihood of uncovering an infectious illness as a cause of chronic urticaria/angioedema is minimal. Nevertheless, there are data in the literature to support investigation under certain circumstances. Laboratory testing depends on the suspected disorder. Laboratory evaluation for hepatitis (A113, B114, and C115) and infectious mononucleosis122,123 might be useful if one of these diseases is suspected. Radiologic evaluation of specific anatomical regions to rule out chronic occult infection is not indicated unless there are convincing supportive clinical data. On rare occasions stool testing for ova and parasites and skin scraping for suspected tinea infection may be helpful.3,120

Autoimmune induction of chronic urticaria/angioedema requires laboratory confirmation. The presence of anti-thyroid peroxidase antibodies in euthyroid or hypothyroid states may implicate an autoimmune etiology.59–61 An evaluation for an underlying autoimmune mechanism may require an anti-nuclear antibody panel. Intracutaneous skin tests with autologous serum may induce a wheal and flare reaction that is suggestive of circulating auto-antibodies to IgE/IgE receptors.87

Tests for malignancy will depend on data accumulated from the history/
physical examination. A chest x-ray\(^{11}\) might confirm the presence of a tumor and/or mediastinal widening in patients with suspected superior venal caval obstruction who present with chronic swelling of the face and neck. A lymphoreticular neoplasm should be suspected\(^{11}\) in patients with cryoglobulinemia and acquired cold urticaria.

A history suggesting a potential occupational cause for chronic urticaria, such as hives occurring when wearing latex gloves, might necessitate laboratory tests such as latex specific in vitro tests for latex proteins and/or skin tests to latex proteins.\(^{13}\)

Venom-specific IgE and IgG RAST and/or venom skin tests should be ordered if the history of insect sting-induced urticaria/angioedema is documented. Serum sickness and/or urticarial vasculitis arising from a hymenoptera sting would require complement assays or other tests for immune complexes. The venom skin tests should be performed or supervised by an experienced allergist/immunologist.

Specific IgE antibody tests (ie, percutaneous skin tests and specific in vitro tests; patch tests read 15 to 30 minutes after application) to suspected antigens\(^{134–139}\) may be useful in confirming a causal relationship between a contactant and induction of urticaria/angioedema. However, contact urticaria is usually acute rather than chronic.

Specific procedures should be ordered if there is a possibility of hyperparathyroidism as causative of chronic urticaria. Appropriate tests would include total calcium, ionized calcium, parathyroid hormone levels and bone density.\(^{128–129}\)

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