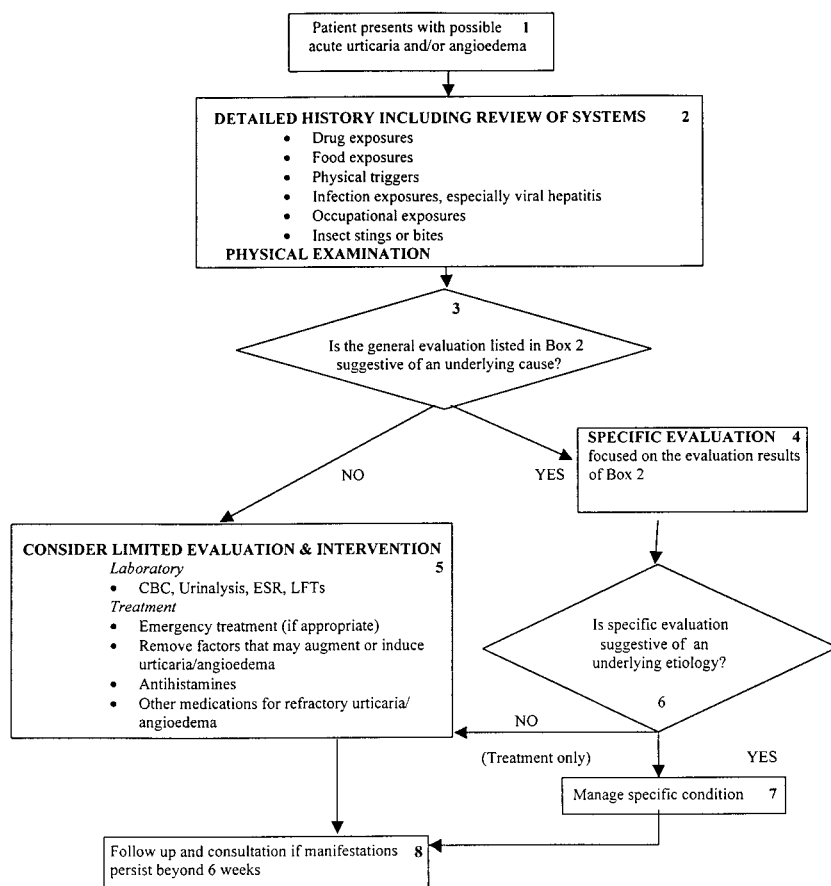


Part 1: Acute Urticaria/Angioedema

ALGORITHM FOR ACUTE URTICARIA/ANGIOEDEMA



The following Annotations are detailed explanations of the Algorithm.

* ANNOTATION 1: Patient presents with possible acute urticaria and/or angioedema

Urticaria and/or angioedema are generally referred to as *acute* if they are of less than 6 weeks duration (see Algorithm for acute urticaria).¹ Acute urticaria occurs more commonly in children and young adults, whereas chronic urticaria is more common in “middle-aged” women.²⁻⁵ It is useful to characterize urticaria as acute in a patient who is experiencing urticaria

for the first time or who has had recurring acute urticarial events, versus the patient who has a history of urticaria for several weeks on a continuous basis. In the former group of patients, the etiology may be readily apparent to both the patient and the physician. For example, the etiology may be obvious in a patient who presents with acute urticaria after drug administration, an insect sting, or repetitively following exposures to cold. If the cause of an acute episode of hives is obvious to both patient and physician, a detailed history and physical are not required. **(Proceed to Annotation 3)** In con-

trast, the longer the urticaria has been continuously present, the more difficult the etiology is to determine.⁶

As many as 15% to 24% of the US population will experience acute urticaria and/or angioedema at some time in their lives.^{7,8} Urticaria should be considered when the patient presents with pruritic (and sometimes painful or burning), erythematous, circumscribed (or coalescent) wheals. Urticarial lesions commonly involve the extremities and trunk but may appear on any part of the body. Angioedema manifests itself as deeper subcutaneous swelling. Less circumscribed than the lesions of urticaria, angioedema has a predilection for areas of loose connective tissue such as the face, eyelids or mucous membrane involving the lips, and tongue. If tissue distention involves sensory nerves, angioedema lesions may be painful or paresthetic.^{2,9} Location and/or duration of the lesions may provide clues to the etiology of the process. Thus, lesions due to cold exposure, exercise or dermatographism typically last less than 2 hours and lesions of urticarial vasculitis appear predominantly on lower extremities and persist without change in morphology for longer than 24 to 48 hours.¹⁰

Clinical presentations of urticaria/angioedema may encompass dermatographism [ie, exaggerated triple response of Lewis (local reddening, edema and surrounding flare)], papular urticaria, localized urticaria, cutaneous and mucosal manifestations of anaphylaxis/anaphylactoid reactions or an underlying disease. Angioedema may occur with or without urticaria. In the latter circumstance, hereditary or acquired C1 esterase inhibitor deficiency should be suspected.

Acute urticaria and/or angioedema may begin suddenly, with physical manifestations appearing over a period of minutes to hours, or may evolve insidiously over a longer period of

time. The evanescent, transient time course of acute urticaria and/or angioedema lesions is characteristic of the process.^{2,11}

If angioedema involves the upper respiratory tract, life-threatening obstruction of the laryngeal airway may occur. Hereditary or acquired angioedema associated with C1 esterase deficiency are particularly prone to this presentation, although other forms of angioedema can present with glossopharyngeal edema causing hoarseness and difficulty in swallowing.^{2,12} Presentations such as this, however, accentuate the importance of evaluating the patient who presents with acute urticaria and/or angioedema for the need of emergency treatment, as urticaria and/or angioedema may be early signs in the evolution of anaphylaxis. A detailed history and physical examination may need to be deferred until emergency treatment has been administered.

*** ANNOTATION 2: Detailed History and Physical Examination**

To maximize the possibility of discovering the specific etiology of acute urticaria and/or angioedema, a detailed history of the circumstances preceding and surrounding the onset of the condition is necessary. This should include, but not necessarily be limited to, the following information: (1) current or previous medications, herbals, or supplements (including excipients) which the patient has used and the time they were started in relationship to the appearance of the lesions; (2) relationship to food exposures (ingestion, inhalation, contact) and the onset of urticaria and/or angioedema;¹³ (3) relationship of potential physical triggers, eg, cold, exercise, heat, sweating, pressure, sun (or light) exposure; (4) exposure to infectious processes, such as a respiratory virus, viral hepatitis, or infectious mononucleosis; (5) occupational exposure to allergens or irritants; (6) any recent insect sting or bite; (7) contact exposure due to high or low molecular weight allergens; (8) allergen exposure by inhalation; and (9) a complete review of systems to include

systemic diseases, such as autoimmune, connective tissue and lymphoproliferative disorders.^{2,14,15-25}

A thorough physical examination should, at a minimum, include examination of the skin, lymph nodes, eyes, joints, throat, neck, ears, lungs, heart, and abdomen in an effort to detect an associated underlying condition (eg, connective tissue disorders, thyroid disease, lymphoreticular neoplasms).^{9,26} (See **Commentary 1**).

*** ANNOTATION 3: Is evaluation suggestive of an underlying cause?**

Specific findings on physical examination or clues developed from the clinical history may direct the evaluation towards an identifiable trigger for the urticaria and/or angioedema. Pertinent infectious exposures, food ingested within several hours prior to the appearance of symptoms several hours after ingestion, medication use preceding the appearance of lesions, or occupational exposures may allow the diagnostic focus to be narrowed to a few suspect triggers. These clues are important given the plethora of potential urticarial triggers and the inherent difficulty in identifying triggers responsible for sporadic urticarial reactions.¹³ (see **Commentary 1**)

On examination, the presence of: thyroid enlargement (suggesting an autoimmune process and/or hormonal dysregulation); lymphadenopathy or visceromegaly (suggesting an underlying lymphoreticular neoplasm); or joint, renal, central nervous system, skin or serous surface abnormalities (suggesting a connective tissue disorder) will similarly focus the evaluation.²⁷ The presence of dermatographism (urtication on stroking of the skin) suggests the presence of a physical urticarial process.^{28,29} Similarly, examination procedures directed to other suspected physical urticarias, (eg, cold, heat or solar urticaria/angioedema) can be employed for diagnosis.³⁰⁻³⁴ Cold, heat, and light tests are available for these respective physical urticarias.³⁰⁻³⁴ Localized hives or edema at pressure sites also point to a physical trigger for the urticarial pro-

cess.¹³ Pinpoint hives after exercise or heat exposure suggest a possible cholinergic process.³⁵ Concomitant manifestations of a more general process (eg, respiratory distress, hypotension, airway obstruction, gastrointestinal distress) accompanying urticaria should immediately redirect attention away from hives as the primary factor to an underlying anaphylactic process which necessitates rapid intervention.

Patients with acute urticaria and/or angioedema may represent a complex, multifactorial, evolving process. Evaluation, diagnosis, and management (both short-term and, if lesions persist beyond 6 weeks, long-term) may be challenging. For these reasons, patients presenting with acute urticaria and/or angioedema, for which the inciting triggers are not clear and easily avoided or initial therapy is not optimally effective, might be considered for referral to an appropriate specialist.

*** ANNOTATION 4: Specific evaluation**

The specific evaluation of a patient presenting with acute urticaria and/or angioedema should focus on the findings suggested by the clinical history and physical examination. Patients with a specific food, drug or insect hypersensitivity should be evaluated with appropriate diagnostic tests. For instance, a patient presenting with acute urticaria in temporal relationship to a specific food, insect sting/bite or drug may warrant in vivo or in vitro assessment of specific IgE (if available) to that particular allergen in a controlled setting where the expertise and equipment needed to treat an anaphylactic reaction are available. If acute mononucleosis is suspected, appropriate tests for Epstein-Barr virus (eg, MonospotTM) could be confirmatory. The association of other infections with acute urticaria has not been sufficiently documented to recommend specific diagnostic tests.^{36,37} A patient presenting with recurrent episodes of acute angioedema of the face, tongue or lips, in association with bouts of severe abdominal discomfort without associated urticaria should be evalu-

ated with specific complement studies to exclude hereditary or acquired C1 esterase inhibitor deficiency. Acute urticaria in association with the administration of penicillin or a related beta-lactam antibiotic may warrant diagnostic evaluation with penicillin skin testing. Allergen skin testing and/or in vitro tests for detection of specific IgE antibody to inhalants (eg, animal danders, pollens, molds, etc) may be useful when the history reveals that urticaria/angioedema occurs after direct contact with a suspected allergen such as direct contact with animals, weeds, and grass. Physical findings of weight loss, lymphadenopathy, and visceromegaly would warrant a further medical evaluation to exclude an underlying lymphoreticular malignancy.

*** ANNOTATION 5: Limited Evaluation/Treatment**

In the absence of historic or physical examination findings leading to a suggested underlying cause, a limited laboratory diagnostic evaluation (including a complete blood count with differential, urinalysis, erythrocyte sedimentation rate, and liver function tests) may be considered, primarily to identify occult underlying conditions at a stage prior to a more overt clinical presentation.²⁶ Concomitantly, or following such evaluation, interventional measures may be implemented. As previously stated, the immediate therapy of acute urticaria and/or angioedema as part of evolving anaphylaxis may necessarily take temporary precedence over diagnostic evaluation. Although there may be increased risks in elderly patients and patients with pre-existing cardiovascular diseases, there are no contraindications to the use of epinephrine in acute life threatening situations. Removal of factors that may augment or induce urticaria/angioedema, (eg, NSAIDs or alcohol ingestion) may result in improvement and would thus seem appropriate in both acute and chronic presentations of urticaria/angioedema.³⁸

Since histamine is one of the primary mediators of urticaria, antihistamine therapy comprises the cornerstone of therapy for acute presentations

of this condition.⁵ Continuous treatment with antihistamines over a period of weeks may suppress the urticarial process until a sustained remission occurs. With the advent of second-generation, low-sedating or non-sedating H₁-antihistamines, the impact of treatment on mental alertness and quality of life can be minimized, primarily through the avoidance of the daytime sedation associated with the use of first-generation H₁-antihistamines.³⁹⁻⁴³ Use of second-generation H₁-antihistamines, (eg, loratadine, fexofenadine, or cetirizine) may be quite effective in controlling the urticarial process without side effects although cetirizine may be mildly sedating in some patients. (see **Commentary 2**). When necessary to achieve optimal hive and pruritus control, as-needed doses of first-generation H₁-antihistamines, (eg, hydroxyzine or diphenhydramine) may be added to or given in place of these agents.⁴⁴ Caution is warranted in carefully building up the dose of older, sedating antihistamines, especially in the treatment of patients involved in occupations that require the operation of machinery or vehicles, or where constant mental alertness cannot be compromised.⁴⁵⁻⁴⁹ To facilitate necessary medication regimen adjustments, an open line of communication between patient and physician is essential during this initial phase of therapy. If optimal doses of H₁-antihistamines do not provide adequate hive control, H₂-antihistamines, (eg, ranitidine or cimetidine) may be added to the regime.⁵⁰ Tricyclic antidepressants such as doxepin, possessing more potent H₁ and H₂-antihistamine properties than some first-generation classical antihistamines, may have a role in therapy, although side effects such as dry mouth may limit their tolerability.⁵¹

The routine use of glucocorticosteroids in the treatment of patients with acute urticaria and/or angioedema is rarely necessary.⁹ When considered essential for acute management, short courses of oral glucocorticosteroids rather than depot parenteral preparations are preferred, to lessen the duration of systemic effects.⁵²

There are preliminary reports about the potential usefulness of leukotriene modifiers in the treatment of chronic urticaria.^{53,54} Until such potential leukotriene-modifying approaches are evaluated in groups of acute urticaria patients, their clinical use remains empirical (although potentially justifiable for patients refractory to conventional therapies or in patients for whom avoidance of glucocorticosteroid therapy is desired).

*** ANNOTATION 6: Is additional evaluation suggestive of underlying etiology?**

In the proper clinical context, the finding(s) of specific, confirmatory laboratory data, [eg, a positive in vitro assay for a food allergen; a low C4 level; abnormal functional/quantitative assays of C1-esterase inhibitor protein; a positive skin test for penicillin; or an abnormal hemogram confirmed by specific hematologic investigations (bone marrow examination, abdominal CT, etc.) supporting the presence of an underlying lymphoreticular malignancy] may verify the initial diagnostic suspicions of particular specific etiologies for the urticarial process. If a cause has not been determined at this point, the associated chronicity and complexity of the underlying process and its clinical management may warrant referral to an appropriate specialist.

*** ANNOTATION 7: Manage specific condition**

When a specific etiology of the urticaria and/or angioedema has been identified, avoidance/elimination of the inciting trigger(s) assumes the central role (eg, avoidance of specific food allergens, drugs, or trauma that induces angioedema in a patient with hereditary or acquired C1 esterase inhibitor deficiency). Although the etiology of acute urticaria and/or angioedema may be easier to discover than that of chronic urticaria and/or angioedema, the cause or causes may still elude identification. The patient should be counseled regarding this issue, emphasizing the benign prognosis of the condition, provided that history, physical ex-

amination, or laboratory features do not suggest a more serious underlying process.

*** ANNOTATION 8: Follow up, if symptoms persist**

The persistence of urticaria and/or angioedema beyond 6 weeks, despite appropriate acute evaluation and intervention necessitates a reorientation towards a chronic process, and may thus warrant further evaluation discussed in the accompanying algorithm on evaluation of chronic urticaria and/or angioedema (**Part II**). At this point, referral to an allergist/immunologist is appropriate, especially if the etiology has not been conclusively determined.

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

COMMENTARY 1: History and Physical Examination

The differential diagnosis of acute urticaria and/or angioedema must be kept at the forefront during the initial evaluation of the patient, as urticaria and/or angioedema, or lesions resembling these processes, may be the initial signs of systemic disease. Evaluation of the urticarial process should be characterized and correlated with associated historical elements.

The following underlying processes, many of which have prominent dermatologic findings, should be differentiated from urticaria.²⁶

Erythema multiforme minor often involves lesions morphologically resembling urticaria, and is triggered by similar underlying disorders, eg, infections, drugs, or neoplasms. A more exaggerated prodromal phase, accompanied by fever, malaise, pharyngalgia, burning or stinging of the lesions and mucosal lesions may develop in those patients who progress to erythema multiforme or the Stevens-Johnson syndrome, potentially fatal processes.

Bullous pemphigoid and dermatitis herpetiformis are both autoimmune bullous/vesiculobullous processes. Early lesions in both diseases are often very

pruritic and clearly have identifiable urticarial components, often resembling lesions of papular or cholinergic urticaria. The symmetry of the lesions of dermatitis herpetiformis, and the progression of the lesions of bullous pemphigoid to typical bullae, usually allow differentiation of these disorders.

Urticaria is often a component of serum sickness which is an IgM/IgG immune complex-mediated hypersensitivity response to drug exposure, insect stings, or heterologous serum administration. Immune complexes in slight antigen excess stimulate anaphylatoxin-mediated histamine release. Arthralgias, fever, and lymphadenopathy are prominent. The time course is slower in onset (days to weeks) than an acute, IgE-mediated anaphylactic response to these same potent triggers. Additionally, the other target organ manifestations of an acute anaphylactic reaction (eg, bronchospasm and hypotension) are not typically present.

Urticarial vasculitis may be restricted to the skin or be part of a systemic immune complex and/or autoimmune disorder. The specific clinical characteristics are individual lesions lasting longer than 24 hours, purpura, bruising, petechiae, livedo reticularis, predilection for the lower extremities (versus trunk or arms), pigmentation of lesions in various stages of healing, ulceration of lesions, predominance of burning and pain (versus pruritus), and systemic or constitutional symptoms such as fever, arthralgia/arthritis, gastrointestinal symptoms, myalgias, malaise, or weight loss. These features allow separation of this entity from a more benign urticarial process.

Mast cell releasability syndromes include (1) cutaneous mastocytosis [ie, urticaria pigmentosa, solitary mastocytoma, diffuse cutaneous mastocytosis (without urticaria pigmentosa), and telangiectasia macularis eruptiva perstans]; (2) systemic mastocytosis with or without skin involvement; (3) mastocytosis in association with hematologic disorders (eg, leukemia); (4) lymphadenopathic mastocytosis with eosinophilia; and (5) mast cell leuke-

mia.⁵⁵ Flushing, hives, itching, bruising, and tingling are common cutaneous symptoms. Systemic symptoms are diverse depending on the amount and degree of visceral mast cell involvement. Darier's sign may be helpful in patients with cutaneous mastocytosis.

The morphology of the urticarial lesions may give clues to the underlying trigger(s). For example, cholinergic urticaria occurs after a rise of body core temperature (eg, after exercise, heat exposure, or fever). The lesions typically begin as small, generally 1 to 3-mm wheals, with large surrounding erythema ("flare"). In contrast, urticaria presenting in association with exercise-induced anaphylaxis characteristically has larger initial wheals. The delayed, point-of-exposure swelling and/or urticaria associated with pressure urticaria presents yet another variation in the appearance of the urticarial process.

Assessment of the prevalence of findings in a series of adult patients with urticaria and/or angioedema showed that urticaria and angioedema were present in tandem in approximately 50% of cases. In 40% of cases, urticaria was present without accompanying angioedema. In the remaining 10%, angioedema was exclusively present.⁶ It is in this latter group that concern should be given to the possibility of either an underlying complement disorder such as a C1 inhibitor deficiency, or a non-immunologically mediated adverse drug reaction such as that seen with angiotensin-converting enzyme inhibitor (ACE) therapy. The concomitant presence of *both* urticaria and angioedema virtually eliminates the possibility of hereditary or acquired C1 esterase inhibitor deficiency. Isolated angioedema in the upper extremities should give rise to the consideration of an obstructive phenomenon such as the superior vena cava syndrome. The systemic capillary leak syndrome, which presents with brawny edema and shock, is an additional differential diagnostic consideration.^{56,57}

A detailed history of infectious exposures, medication use (both prescription, over-the-counter, herbal, and other unconventional types), use of vitamins and dietary supplements, and food ingestion temporally related to the appearance of lesions is important.⁵⁸ Acute infections in children may be associated with acute urticaria.^{36,37,59}

Epstein-Barr virus (EBV), hepatitis (A, B, and C),⁶⁰⁻⁶³ and gastrointestinal parasites have been implicated anecdotally in the causality of urticarial reactions. Food proteins incriminated in the precipitation of acute allergic urticaria include peanuts, nuts, fish, shellfish, wheat, eggs, milk, soybeans, and fruits. Food additives such as benzoates, sulfites, monosodium glutamate, butylated hydroxyanisole, butylated hydroxytoluene, FD&C approved dyes and others have been implicated in some cases of urticaria.⁶⁴⁻⁶⁶ Non-immunologic high content of or release of histamine causing hives and flushing may occur after ingestion of strawberries, cheese, spinach, eggplant, lobster, and tomatoes.⁶⁷ Bacterial conversion of histidine to high levels of histamine may occur in contaminated scombroid fish (eg, tuna, mackerel). Among the most common medication triggers of urticaria are penicillin, other beta-lactam antibiotics, opiates, radiocontrast media, aspirin, insulin, and many other non-beta lactam drugs and biologics. [See **Disease Management of Drug Hypersensitivity: A Practice Parameter (Ann Allergy Asthma Immunol 1999;83:S665-S700)**].

A social and travel history should be obtained to highlight possible infectious exposures encountered during travel, or acute allergen exposures in the patient's home or workplace. Occupational history may discover contact allergen exposure (eg, chromates in the cement industry, latex, other rubber products, and cosmetics) amenable to identification by patch testing with the appropriate allergen(s).⁶⁸⁻⁷⁰ Exposure to plants and common aeroallergens may suggest a source of symptoms secondary to contact exposure.⁷¹⁻⁷⁵

COMMENTARY 2: Representative Agents and Doses for the Treatment of Acute Urticaria

Cetirizine (Zyrtec):
5 to 20 mg, once daily or occasionally in divided doses especially if somnolence is not a problem†

Loratadine (Claritin):
5 to 10 mg once daily in AM

Fexofenadine (Allegra):
180 mg given once daily or 60 mg twice daily

Hydroxyzine HCl (Atarax or Vistaril):
10 to 100 mg daily often at bedtime or in divided doses, titrated to effect or somnolence.

Diphenhydramine (Benadryl):
12.5 to 100 mg per dose q4 to 6 hour PRN

Doxepin: (Sinequan)
Adults: 25 to 100 mg/day
Adolescents: 25 to 50 mg/day initially up to a maximum of 100 mg/day
Children: 1 to 3 mg/kg/day

†Julian L. et al. Cetirizine in the treatment of chronic urticaria Clin Ther 1991;13:81-85.

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