Urticaria: A comprehensive review

Epidemiology, diagnosis, and work-up

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Learning objectives
After completing this learning activity participants should be able to recognize the various type of urticaria; recall diagnostic strategies for confirming the diagnosis; and describe the key histopathology features involved in the diagnosis of urticaria.

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Urticaria is a common clinical condition presenting with wheals (hives), angioedema, or both. Urticaria has a complex pathogenesis, along with a high disease burden, a significant impact on quality of life, and high health care costs. The first article in this continuing medical education series covers the definition, classification, epidemiology, diagnosis, and work-up of urticaria, taking into account the recent literature and the best available evidence. (J Am Acad Dermatol 2018;79:599-614.)

Key words: acute; angioedema; chronic physical urticaria; histopathology; hives; inducible urticaria; testing; urticaria; wheals.

Urticaria presents with wheals (hives), angioedema, or both, and has a lifetime prevalence of about 9%.[1,2] The appearance of pruritic, erythematous dermal swellings that blanch with pressure, indicating the presence of vasodilation and superficial dermal edema, is characteristic of wheals.[3] Angioedema is caused by similar pathologic alterations that occur in the reticular dermis and subcutaneous tissue, with poorly defined swelling and burning.[4] One-third of patients present with both hives and angioedema, 30% to 40% present with isolated hives, and 10% to 20% with isolated angioedema.[1,5,6]

Abbreviations used:

ASST:	autologous serum skin test
AU:	acute urticaria
CSU:	chronic spontaneous urticaria
CsA:	cyclosporine
CU:	chronic urticaria
DPU:	delayed pressure urticaria
NSAID:	nonsteroidal antiinflammatory drug

The spinothalamic tract is thought to play an important role in the pathway of pruritus.[7] Primary afferent neurons, also known as pruriceptors, detect itch-inducing substances like histamine and chloroquine.[8] The most well-known pruritogen is

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histamine; however, non-histaminergic mediators also exist.[9] Initially it was thought that the nerve fibers only responded to histamine/nonhistamine stimulus, but it is now accepted that these fibers can also be stimulated by noxious stimuli.[7]

Urticaria has a complex pathogenesis and a significant impact on quality of life.[1,10] Urticaria-related costs may be as high as $1750 to $2050 per patient per year.[11,12]

CLASSIFICATION

Key points

- **Urticaria cases are classified as either acute or chronic**
- **Chronic urticaria is defined if daily or almost daily wheals or angioedema are present for >6 weeks**

Urticaria can be classified according to duration and etiology,[13] although ≥2 types of urticaria can coexist in the same patient (Table I).

Table I. Classification of urticarias*

Type	Clinical feature or type
Acute urticaria	
Chronic urticaria	
Chronic spontaneous urticaria	Spontaneous appearance of itchy wheals, angioedema, or both for ≥6 weeks because of known[†] or unknown causes
Chronic inducible urticaria	
Physical urticaria	Symptomatic dermographism[‡]
	Cold urticaria[§]
	Delayed pressure urticaria[¶]
	Solar urticaria
	Heat urticaria[#]
	Vibratory angioedema
Other inducible urticaria	Cholinergic urticaria
	Contact urticaria
	Aquagenic urticaria

*Modified from data presented by Zuberbier et al[13] and Margerl et al.[14]
[†]For example, autoreactivity; that is, the presence of histamine-releasing autoantibodies (also called urticaria factitia).
[‡]Dermographic urticarial.
[§]Cold contact urticarial.
[¶]Pressure urticarial.
[#]Heat contact urticaria.

ACUTE URTICARIA

Key points

- **Acute urticaria has precipitating factors in <50% of cases**
- **When present, the most common triggers are infections, drug reactions, and food intolerance**

Acute urticaria (AU) is defined by the occurrence of spontaneous wheals or angioedema for <6 weeks.[13] In acute cases, it is important to exclude anaphylaxis in the presence of respiratory, gastrointestinal, or neurologic symptoms or hemodynamic instability.

Eliciting factors have been found in <50% of cases, with upper respiratory infections being the most common trigger (40%), followed by drug reactions (9.2%) and suspected food intolerance (0.9%).[15] Among infectious agents, upper respiratory tract agents, *Mycoplasma pneumonia*, and parasitic infections have been commonly reported in children,[16] while viral hepatitis and infectious mononucleosis are important culprits in adults.[17-19]

CHRONIC URTICARIA

Key points

- **Chronic urticaria may be subclassified into chronic spontaneous urticaria or chronic inducible urticaria**
- **Up to 30% of cases are associated with functional immunoglobulin G antibodies to the high-affinity immunoglobulin E receptor FcεRIα or to immunoglobulin A**
- **Among patients in which an etiology is suspected, infections, drugs, food, and psychological factors are the most commonly associated**
- **Chronic inducible urticaria is characterized by its ability to be triggered consistently and reproducibly in response to a specific stimulus**

Episodes of daily or almost daily wheals or angioedema lasting for ≥6 weeks are designated as chronic urticaria (CU).[13,20] CU must be distinguished from acute intermittent urticaria/angioedema, where episodes only last hours or days but recur over months or years.[21]

Chronic inducible urticaria (CIndU) represents a subgroup of CU where urticaria is induced by a determined stimulus rather than occurring spontaneously. If no inducible factor is present, the process is termed chronic spontaneous urticaria (CSU). Among this subgroup, 30% to 40% of patients present with autoantibodies, suggesting an autoimmune basis. These cases would be categorized as chronic autoimmune urticaria (CaU) (European guidelines) or as antibody-associated CU (US guidelines).[22]

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