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Decision Making in SKIN ALLERGIES

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SECTION

1

Urticaria

Section Editors: Kiran Godse and Anant Patil

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Introduction and Classification of Urticaria

Natasa Teovska Mitrevska, Vesna Trajkova, Hristina Breshkovska

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DEFINITION AND CLINICAL PRESENTATION

Urticaria, commonly known as hives, has been recognized since ancient times. However, it is only in the last century that we have gained a clearer understanding of its various forms and complexity. It is an inflammatory condition driven by mast cells.[1]

It significantly affects patients beyond the skin, causing pain, sleep disturbances, fatigue, and substantial psychological impact, including anxiety and depression. Untreated urticaria can lead to significant direct and indirect healthcare costs, as well as a reduced quality of life.[2] The condition often impacts physical function, emotional well-being, sexual relationships, social interactions, and work performance. This highlights the importance of timely diagnosis and effective treatment.

Urticaria is characterized by wheals (hives), angioedema, or both:[1]

- "Wheals" are sharply circumscribed, superficial swellings of varying size and shape, surrounded by erythema. They are usually itchy or sometimes cause a burning sensation and typically resolve within 1–24 hours **(Figs. 1 and 2)**.[1,2]
- "Angioedema" involves deep swelling in the lower dermis, subcutis, or mucous membranes. It is often erythematous or skin-colored and is accompanied by tingling, burning, tightness, and occasionally pain, rather than itching. The skin generally returns to normal within 72 hours **(Fig. 3)**.[1-3]



FIG. 1: Wheals on the neck.



FIG. 2: Wheals on lower extremities.



FIG. 3: Angioedema on upper lip.

CLINICAL CLASSIFICATION

Urticaria classification is based on duration and triggers, following the Global Allergy and Asthma European Network (GA^{2}LEN)/the European Academy of Allergology and Clinical Immunology (EAACI)/the World Allergy Organization (WAO)/the European Dermatology Forum (EDF) guidelines (2023) **(Table 1 and Flowchart 1)**.

Acute Urticaria Overview

Repeated appearance of wheals with or without angioedema lasting up to 6 weeks. Acute urticaria has a lifetime prevalence of approximately 20%.[1,4,5]

Key mediators include histamine, platelet-activating factor, and cytokines. These substances cause blood vessels to dilate and become leaky, leading to fluid accumulation in surrounding tissues and activating sensory nerves. Angioedema, a deeper swelling, can be caused by bradykinin release.[1,6]

TABLE 1: Classification of urticaria based of duration and triggers and frequency.[1-3]

	Duration	Frequency
Spontaneous urticaria:		

• Acute urticaria
• *Chronic urticaria*:
  ○ Chronic continuous urticaria
  ○ Chronic recurrent urticaria
	• <6 weeks
	• >6 weeks
	• Daily or on most days of the week
	• Symptom free intervals ranging from days to weeks
	• Eliciting factor
		• Spontaneous wheals appearing most days
		• Spontaneous appearance of wheals

Physical urticaria:		
• Dermographic urticaria • Delayed pressure urticaria • Cold contact urticaria • Heat contact urticaria • Solar urticaria • Vibratory urticaria/angioedema	• Mechanical shearing forces (wheals arising after 1–5 minutes) • Vertical pressure (wheals arising with a 3–8 hours latency) • Cold air/water/wind • Localized heat • Ultraviolet (UV) and/or visible light • Vibratory forces, e.g., pneumatic hammer	
Special types of urticaria:		
• Cholinergic urticaria • Adrenergic urticaria • Contact urticaria (allergic or pseudoallergic) • Aquagenic urticaria		
Different diseases related to urticaria for historical reasons:		
• Urticaria pigmentosa (mastocytosis) • Urticarial vasculitis • Familial cold urticaria (a vasculitis)		

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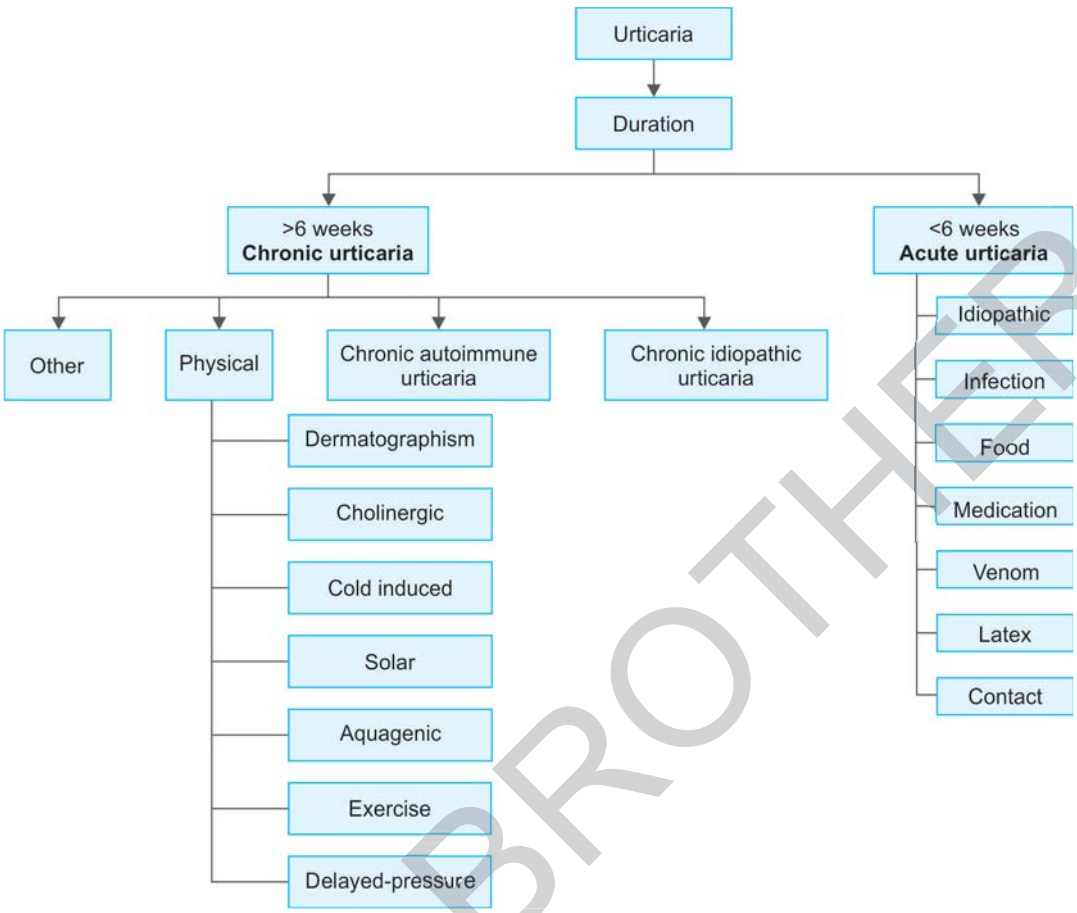

FLOWCHART 1: Classification of urticaria based of duration and triggers and frequency.

Possible Causes of Acute Urticaria

- *Infections*:
  - *Viral*: Upper respiratory infections, viral hepatitis, and infectious mononucleosis.
  - *Bacterial*: Conditions such as dental abscesses, sinusitis, and mycoplasma infections.
- *Allergies*:
  - *Food allergies [immunoglobulin E (IgE)-mediated]*: Common triggers include milk, eggs, peanuts, and shellfish.
  - *Drug allergies (IgE-mediated)*: Often caused by antibiotics.
- *Pseudoallergies*:
  - *Drugs*: Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), opiates, and radiocontrast media. These can trigger urticaria without immune activation.
- *Other triggers*:
  - Vaccination
  - *Insect stings*: Bee or wasp stings.
  - *Localized contact urticaria*: For example, rubber latex, which can cause a widespread reaction.

Complications

Severe cases of urticaria can lead to anaphylactic shock, characterized by bronchospasm and collapse.

Angioedema without Urticaria

May occur as a side effect of angiotensin-converting enzyme (ACE) inhibitors, which can cause recurrent episodes of swelling without the typical hives.

Understanding these factors helps in diagnosing and managing acute urticaria effectively.[1,7,8]

Chronic Urticaria Overview

Recurrence of symptoms beyond 6 weeks. Chronic urticaria can be further divided into chronic spontaneous urticaria (CSU no definite eliciting factor involved) and chronic inducible urticaria (CIU specific definite factor involved). In some cases, angioedema may be the primary or sole manifestation. CSU or CIU can be disabling, impair quality of life, and impact work and school performance. The duration of the disease can vary, and it may persist for several years in CSU cases.[1,3,9]

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Proper classification of urticaria subtypes is crucial for accurate diagnosis, effective treatment, and research interpretation. Most subtypes profoundly impact quality of life, making effective management essential when no treatable cause is identified.[10,11]

URTICARIA DISTINCTIONS

Certain conditions that can present with wheals and/or angioedema are not classified as urticaria due to their distinct pathophysiological mechanisms and clinical presentations.[1,10,11] These include:

- *Urticarial vasculitis*: A form of vasculitis where wheals are associated with inflammation of blood vessels.
- *Maculo-papular cutaneous mastocytosis (formerly known as urticaria pigmentosa)*: Characterized by the presence of mast cell proliferation in the skin.
- *"Indolent systemic mastocytosis" with skin involvement*: A type of mastocytosis where systemic mast cell proliferation affects the skin.
- *Mast cell activation syndrome (MCAS)*: A condition involving episodic mast cell activation with symptoms similar to those of urticaria but driven by different mechanisms.
- *"Autoinflammatory syndromes" (e.g., cryopyrin-associated periodic syndromes or Schnitzler's syndrome)*: Conditions with periodic fever and systemic inflammation that can sometimes mimic urticaria.
- *"Non-mast cell mediator-mediated angioedema" (e.g., bradykinin-mediated angioedema)*: Angioedema caused by factors unrelated to mast cell activation, such as bradykinin.

These conditions are distinct from urticaria due to their unique underlying mechanisms and clinical features.

EVALUATION AND MONITORING

Wheal size can sometimes indicate the severity of urticaria: larger wheals may signal more severe and difficult-to-treat cases. Wheal color can also aid in diagnosis. Lighter-colored wheals with pink erythema suggest histamine involvement, with the pink hue resulting from the dilation of cutaneous vessels. Conversely, dark red or violaceous wheals are often associated with vascular damage and leakage, which may indicate urticarial vasculitis.[1,12]

It is also essential to monitor disease intensity and wheal appearance throughout treatment. Comparing conditions before and after treatment can provide valuable insights into the disease's underlying course. This evaluation should ideally include assessing the quality of life using specialized instruments for urticaria.

Urticaria is characterized by specific triggers that can induce wheals, angioedema, or both.

These triggers are considered definite because wheals, angioedema, or both consistently occur in their presence and never in their absence. They are also subtype-specific, meaning each subtype of inducible urticaria has its own unique trigger—such as cold for cold urticaria—that does not apply to other forms. In rare cases, certain subtypes of inducible urticaria require a combination of two or more specific triggers to induce wheals or angioedema, such as in cold-induced cholinergic urticaria.[4]

Some patients with spontaneous urticaria may also experience trigger-induced wheals or angioedema, but these triggers are not definite. Their presence does not consistently lead to symptoms, and wheals or angioedema can still occur spontaneously without these triggers.[8]

The spectrum of clinical manifestations of different urticaria subtypes is very wide.

Additionally, some patients may exhibit more than one subtype of urticaria, and each subtype may respond independently to treatment.[1]

CONCLUSION

Urticaria, commonly known as hives, is a multifaceted condition with a broad range of clinical presentations, including wheals, angioedema, or both. Its impact on patients extends beyond the skin, affecting emotional well-being, quality of life, and daily functioning. Acute urticaria typically resolves within 6 weeks, while chronic urticaria persists longer and may be either spontaneous or induced by specific triggers. Proper classification of urticaria subtypes is essential for effective diagnosis and treatment, as well as for monitoring disease progression. Identifying triggers and understanding underlying mechanisms are key to developing personalized treatment plans. Management of urticaria requires a comprehensive approach to address its diverse manifestations and improve patient outcomes. Given its significant effect on quality of life and potential complications, timely diagnosis and intervention are crucial.

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1.2

CHAPTER

Acute Urticaria

Michael Rudenko

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INTRODUCTION

According to the international the European Academy of Allergology and Clinical Immunology (EAACI)/the Global Allergy and Asthma European Network (GA²LEN)/the European Dermatology Forum (EDF; EuroGuiDerm)/the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) guideline, the prevalence of acute urticaria in a lifetime is around 20% ranging between 12 and 23.5% with a cumulative incidence of 18.7%.[1,2] It is a common condition, that can occur in all age groups and can be diagnosed by multiple specialists as a separate nosology or can be accompanied by angioedema.[3] Distinguishing between anaphylaxis and acute urticaria/angioedema can be challenging, especially in emergency and primary care settings where prompt and accurate diagnosis is crucial for appropriate treatment. Both conditions involve mast cell and basophil degranulation, leading to the release of histamine and other inflammatory mediators, which can result in similar skin manifestations and angioedema.[2] Acute urticaria being associated with viral infections or has an immunoglobulin E (IgE)-mediated mechanisms in response to medication, food, or an insect sting usually lasts under 6 weeks and is typically self-healing in a few days or weeks.[2,4]

Urticaria presents with a sudden appearance of erythematous patches with pruritus. The underlying mechanism is associated with degranulation of skin mast cells while the generalized mast cell and basophil degranulation causes anaphylaxis. Besides, acute urticaria and angioedema present as the most prevalent symptoms from the skin in anaphylaxis; thus, in emergencies and in primary healthcare setting the differential diagnosis among anaphylaxis and acute urticaria/angioedema is confusing and puzzling in many cases, leading to errors and delayed treatment as adrenaline is the first-line treatment for anaphylaxis, but not for acute urticaria, where H1-antihistamines are the first choice.[5]

Acute spontaneous urticaria results from hypersensitivity toward the allergens resulting in the formation of IgE antibodies that bind to receptors found on mast cells and basophils.

*This **Box 1** outlines an evaluation process for acute urticaria, emphasizing on the consideration of cofactors, duration, triggers, associated conditions, and management strategies. It serves as a visual aid for understanding the diagnostic approach to this common dermatological condition.*

Physical factors known as cofactors include exercise exceeding the standard daily routine, alcohol, nonsteroidal anti-inflammatory medication, and heat or change in temperature, as well as other factors that can range from increased stress levels, changes in hormonal levels (menstruation), or consequences of an infection. Genetic background may contribute in creating clinically relevant predisposition to particular conditions.[6]

The presence of cofactors may explain why some patients can tolerate an allergen in some circumstances but in others the same patients develop a severe anaphylactic reaction that can appear immediately after a contact with respective allergens and allergy tests may help to avoid re-exposure to relevant causative factors. Cofactors can influence basophils and mast cells, leading to mediator release. In the presence of certain cofactors, less quantity of allergen might be required to cause clinical symptoms.[7]

Cofactors, including exercise and alcohol, might lower the threshold for IgE-mediated mast cell degranulation, increase allergen permeability in the gastrointestinal tract and osmolality, and redistribute blood flow.

BOX 1 Evaluation process for acute urticaria.

- *Presenting symptoms*: Sudden onset of erythematous areas with pruritus
- *Co-factors in acute urticaria*:
  - Exercise
  - Alcohol
  - Nonsteroid anti-inflammatory drugs (NSAIDs)
  - Heat or temperature changes
  - Stress
  - Menstruation
  - Infection
- *Duration*: <6 weeks
- *Mechanism*:
  - Mast cell and basophil degranulation due to allergen hypersensitivity
  - Immunoglobulin E (IgE)-mediated response
- *Triggers*:
  - Allergens (e.g., food, medication, and insect stings)
  - Viral and bacterial infections
  - Coronavirus disease 2019 (COVID-19) and other respiratory tract infections
- *Associated conditions*:
  - Angioedema
  - Urticarial vasculitis
  - Delayed anaphylaxis (e.g., α-gal syndrome, ω-5 gliadin sensitivity)
- *Management*:
  - Antihistamines (H1-antihistamines) as first-line treatment
  - Avoidance of triggers, if identified
  - Consideration of additional therapies for refractory cases

We suggested an evaluation process for acute urticaria, emphasizing on the consideration of cofactors, duration, triggers, associated conditions, and management strategies **(Box 1)**.

The best-known mediator contained in mast cells is histamine 2-(4-imidazolyl)-ethylamine, but it is not the only one. The effects of other mediators are significant in mast cell-mediated conditions, and can be future therapeutic targets.[8]

Upon re-exposure, the allergen is recognized by cell-bound specific IgE, leading to receptor crosslinking. This event leads to the release of many immune-mediating enzymes, primarily histamine which causes increased capillary permeability that is presented in the form of swelling on the upper dermal layer of the skin cases of acute urticaria and urticarial vasculitis were reported in association with COVID-19, and influenza A/H1N1 infection.[9,10]

Acute urticaria and angioedema apart from being a symptom of allergic reactions to medications, venoms, and food, can also be present in association with a range of viral and bacterial infections.[3] Acute urticaria and angioedema were reported in addition to respiratory symptoms in COVID-19.[2,4] COVID-19 and other viral infections, in particular, respiratory tract infections can trigger the onset of acute urticaria either occurring concurrently with the infection or in some cases proceeding the infection. Acute urticaria, possibly associated with circulating autoantibodies, was shown to become chronic in 5–39% of the cases.[11]

Urticaria and angioedema were also described as a part of delayed anaphylaxis in people sensitized to galactose-α-1,3-galactose (α-Gal) following tick bites.[12]

Conditional reactions ranging from urticaria and angioedema to even anaphylaxis can occur when sensitized patients to ω-5 gliadin in gluten get exposed to gluten in a presence of a co-factor (stress, exercise, and nonsteroidal anti-inflammatory drugs heat or change of temperature and alcohol).[13,14]

In urticarial vasculitis unlike in urticaria the rash is more persistent (lasting >24 hours) followed by residual bruising.[15,16] Urticarial vasculitis with systemic manifestations can be contributed to presence of circulating anti-C1q autoantibodies and reduction of serum complement levels.[17]

CONCLUSION

Acute urticaria occurs in up to 20% of individuals. It is a condition characterised by sudden pruritic erythematous lesions, often linked to IgE-mediated triggers or infections. Distinguishing acute urticaria from it being a symptom of anaphylaxis remains critical, as both involve mast cell activation, but later requires urgent intervention. Cofactors like NSAIDs, stress, or infections can lower the stability thresholds, exacerbating symptoms. Management plan can include trigger avoidance, H1-antihistamines, and addressing underlying infections. Emerging associations with COVID-19, urticarial vasculitis, and delayed anaphylaxis (e.g., α-gal syndrome) underscore the need for vigilant evaluation. Future research into the role of non-histamine mediators may refine therapeutic strategies, improving outcomes for this transient yet complex disorder.

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1.3

CHAPTER

Chronic Urticaria and Its Types

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INTRODUCTION

Urticaria is a common condition characterized by the presence of wheals and/or angioedema. Wheals typically present as central edema surrounded by reflex erythema, often accompanied by itching or a burning sensation, and individual lesions generally resolve within 24 hours. Angioedema, on the other hand, is marked by swelling that can persist for up to 72 hours and may be associated with pain and burning.

CLASSIFICATION

Urticaria is classified based on the duration of symptoms: Acute urticaria lasts less than 6 weeks, while chronic urticaria persists for 6 weeks or longer. Chronic urticaria can be further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). In CSU, wheals and/or angioedema occur spontaneously, without any identifiable trigger.[1] Conversely, in CIndU, these symptoms arise only after exposure to specific triggering factors, which may include various physical stimuli or specific urticariogenics, as seen in contact urticaria **(Fig. 1 and Flowchart 1)**.[2]

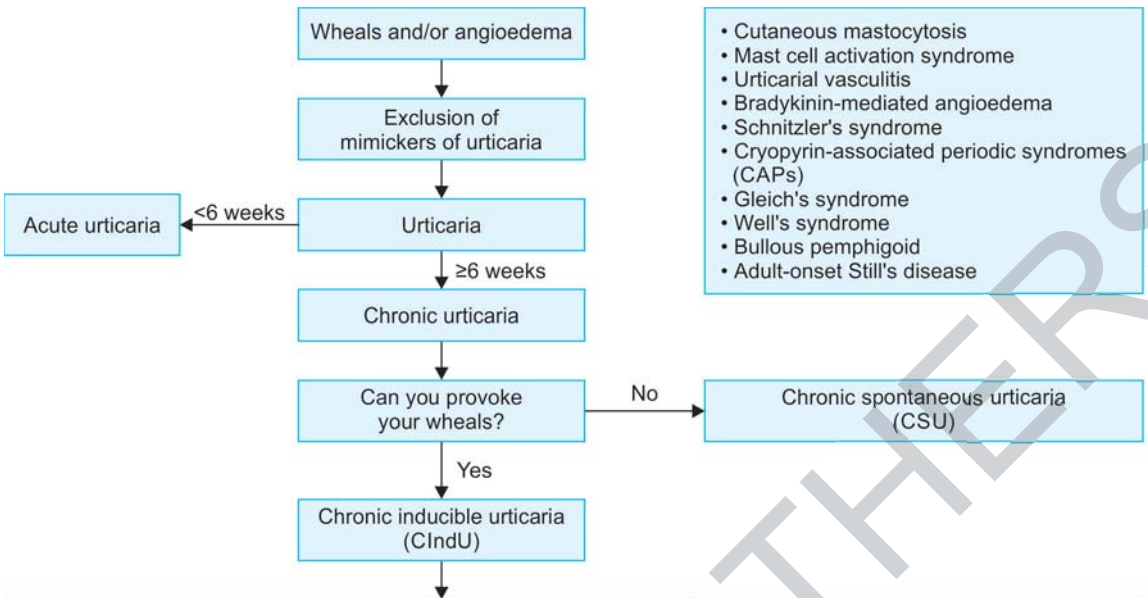
Chronic inducible urticarias encompass a range of conditions, including symptomatic dermographism, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, vibratory angioedema, cholinergic urticaria, aquagenic urticaria, and contact urticaria. It is possible for a patient to experience one or more types of CIndU and/or CSU simultaneously. A thorough medical history, coupled with the question, "Can you provoke your wheals?" is essential for diagnosing CIndUs. To confirm the diagnosis, assess the threshold levels that provoke wheals, and evaluate the response to treatment, standardized provocation tests should be employed.[3]



FIG. 1: Wheals in a patient with chronic spontaneous urticaria.

CONCLUSION

Although urticaria is typically a straightforward diagnosis, differential diagnoses should be carefully considered, especially in cases with atypical wheal characteristics. Once urticaria is diagnosed, it should be classified according to the updated nomenclature, which is based on symptom duration and potential triggering factors.



Type of CIndU	Triggering factor	Provocation test
Symptomatic dermographism	Shearing forces on the skin	FricTest,® Dermographometer
Cold urticaria	Cold air, objects and liquids	Ice cube test, TempTest,® Cold water baths
Heat urticaria	Contact heating of the skin	Hot water baths, TempTest®
Delayed pressure urticaria	Pressure on the skin	Weighted rods
Solar urticaria	Exposure to sunlight	UVA/UVB irradiation, Visible light
Vibratory angioedema	Exposure to vibration	Vortex vibrator
Cholinergic urticaria	Elevation of body temperature due to exercise or hot bath, etc.	Pulse-controlled ergometry
Aquagenic urticaria	Exposure to water	Compress or towel soaked with water 35–37°C
Contact urticaria	Various urticariogenics	Open controlled application testing

FLOWCHART 1: Chronic urticaria and its types.

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