Approach to urticaria and angioedema

VGH CTU SUBSPECIALITY ROUNDS

APRIL 16, 2025

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Disclosure Slide

Honoraria/Ad board:

- AstraZeneca
- Sanofi
- Arcutis
- Novartis
- Medexus
- ALK
- Miravo
- Stallergenes
- Takeda

Objectives

Review clinical features of urticaria and angioedema that differentiate them from other presentations

Develop an approach to diagnosis of urticaria and angioedema

Understand guideline level recommendations for treatment options in urticaria and angioedema

Case 1

Angela is a 28 year-old woman who presents with a 6 month history of **intermittent rash** on the body. She has also been having episodes of **lip and eye swelling**. It started after she got the COVID-19 vaccine. The rash is very bothersome, and she is unable to sleep well. There has partial improvement with use of cetirizine PRN.

Is this angioedema?

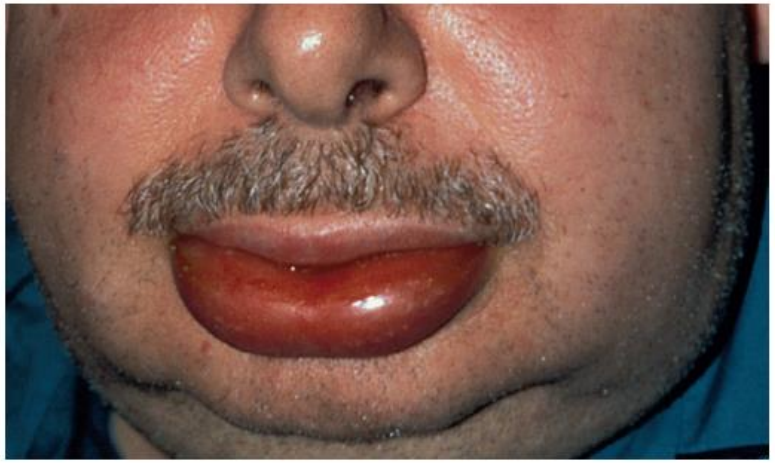
Angioedema

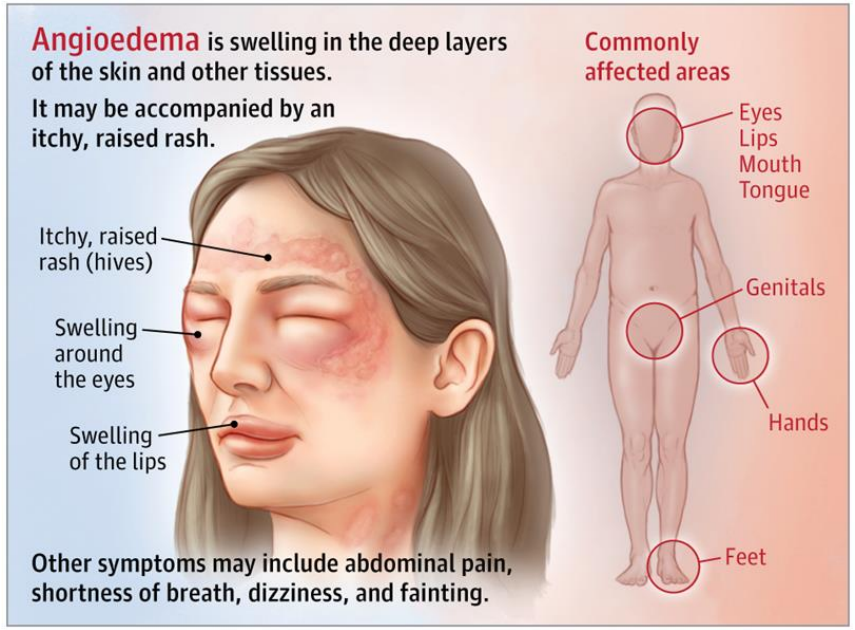
What makes swelling angioedema?

Clinical Features

Angioedema:

- **Non-pitting, skin-coloured edema** of deep dermis, subcutaneous and submucosal tissues
- May present with sensation of pain rather than itch
- Caused by increased vascular permeability
- Duration of swelling dependent on underlying mechanism





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Tarbox JA, Bansal A, Peiris AN. Angioedema. JAMA. 2018;319(19):2054. doi:10.1001/jama.2018.4860

Not angioedema?

Review

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2016;169:163–170
DOI: 10.1159/000445835

Published online: April 22, 2016

How Not to Be Misled by Disorders Mimicking Angioedema: A Review of Pseudoangioedema

Michelle Fog Andersen[a] Hilary J. Longhurst[d] Eva Rye Rasmussen[b]
Anette Bygum[c]

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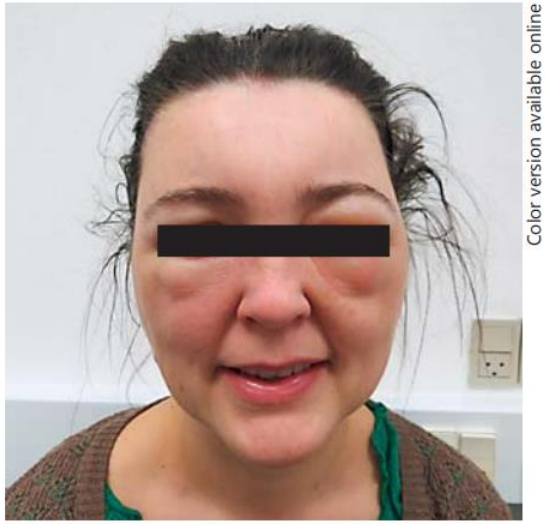

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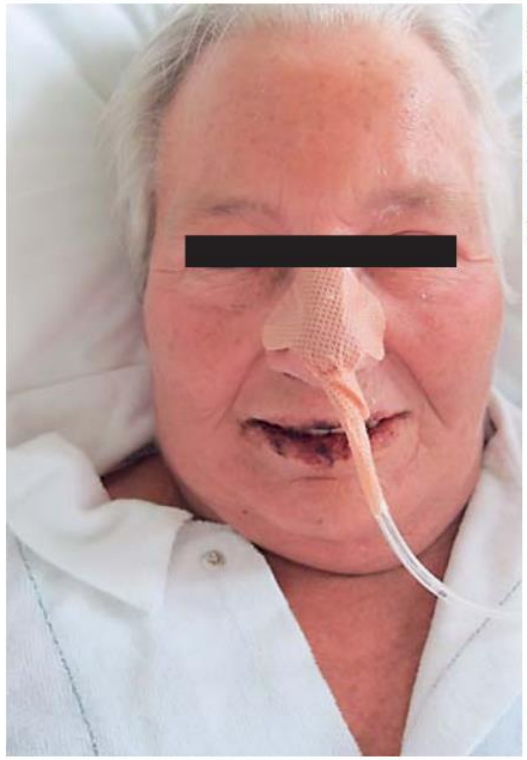

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Fig. 1. Acute contact dermatitis with severe facial swelling after hair dyeing.
Fig. 2. Generalized edematous swelling and morbilliform rash in a patient with DRESS.

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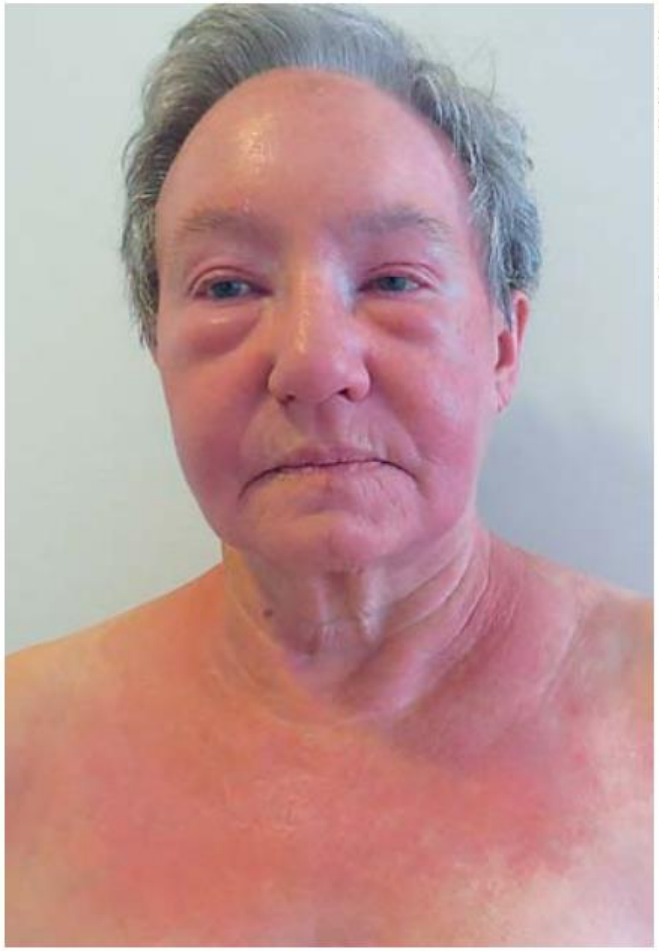

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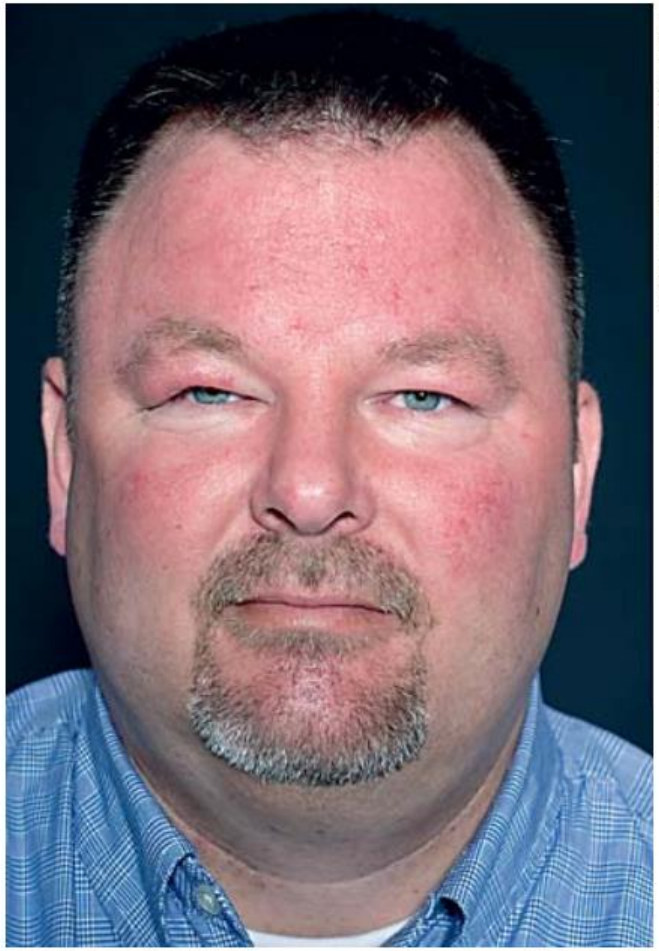

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Fig. 3. Heliotrope rash and edema and rash in the shawl area in a patient with dermatomyositis.

Fig. 4. Persistent swelling of the forehead, cheeks and upper eyelids in a patient with Morbus Morbihan.

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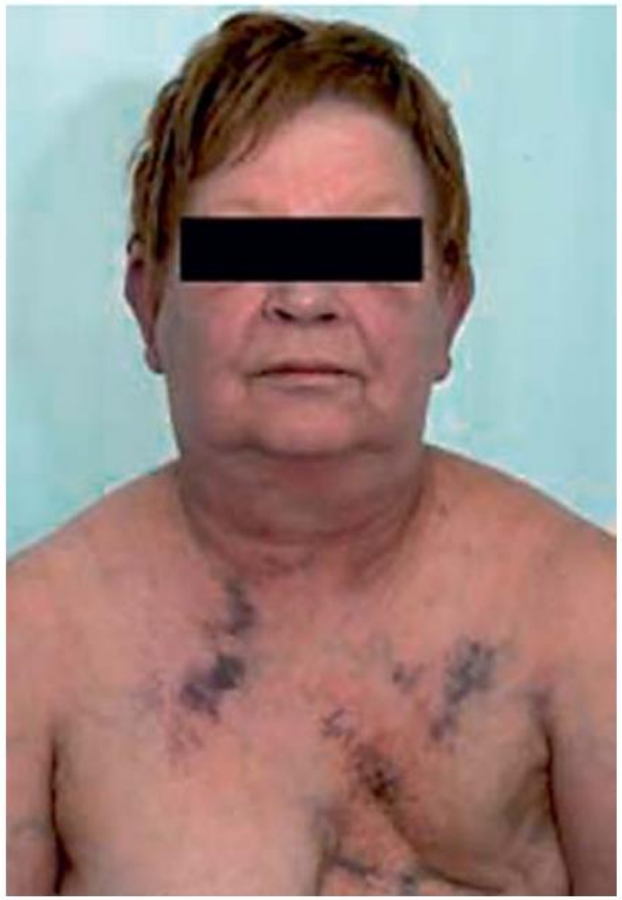

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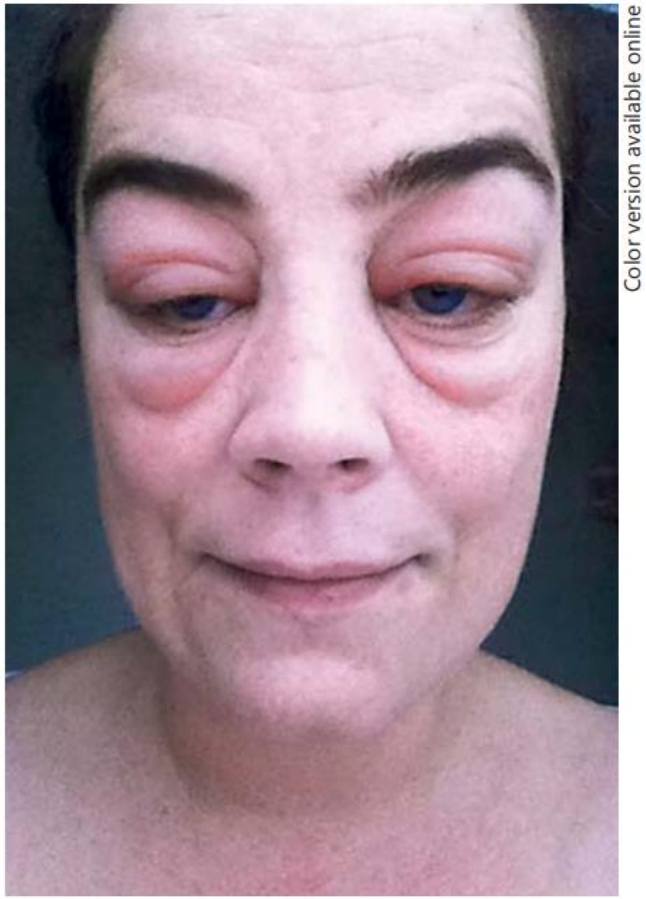

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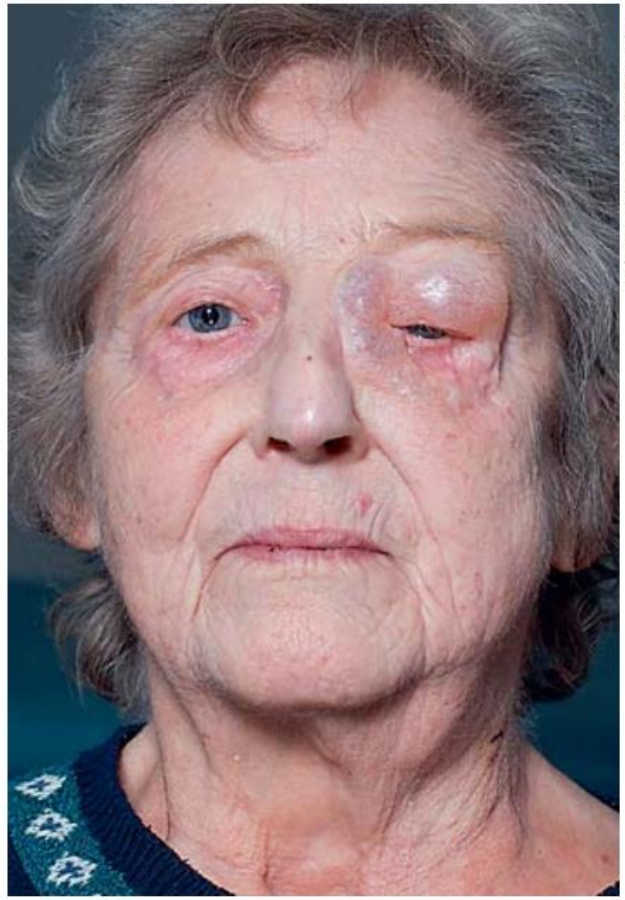

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Fig. 5. Facial and neck swelling accompanied by dilatation of veins and cyanosis in a patient with superior vena cava syndrome. Photo credit: Tarec Christoffer El-Galaly, MD, and Nina Keldsen, MD, reprinted with permission [Ugeskr Læger 2007;169:3118].
Fig. 6. Severe manifestation of periorbital edema in a patient with hypothyroidism.
Fig. 7. Subcutaneous emphysema with severe swelling of the left chin, eyelids and neck after a simple dental procedure.

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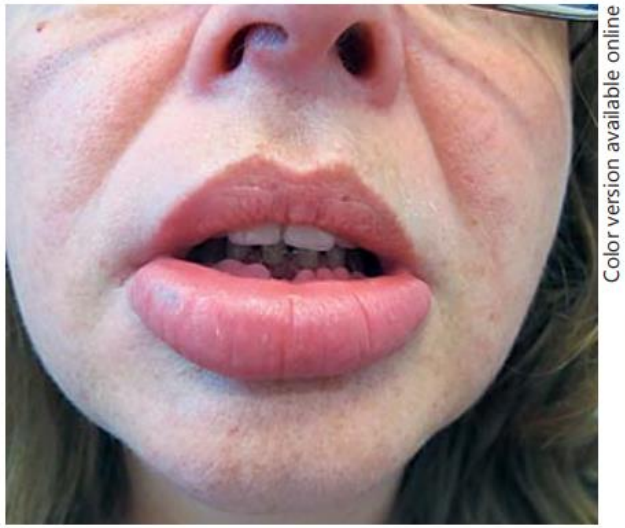

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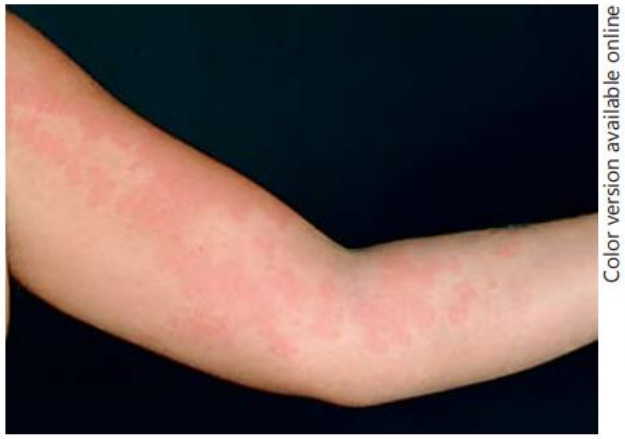

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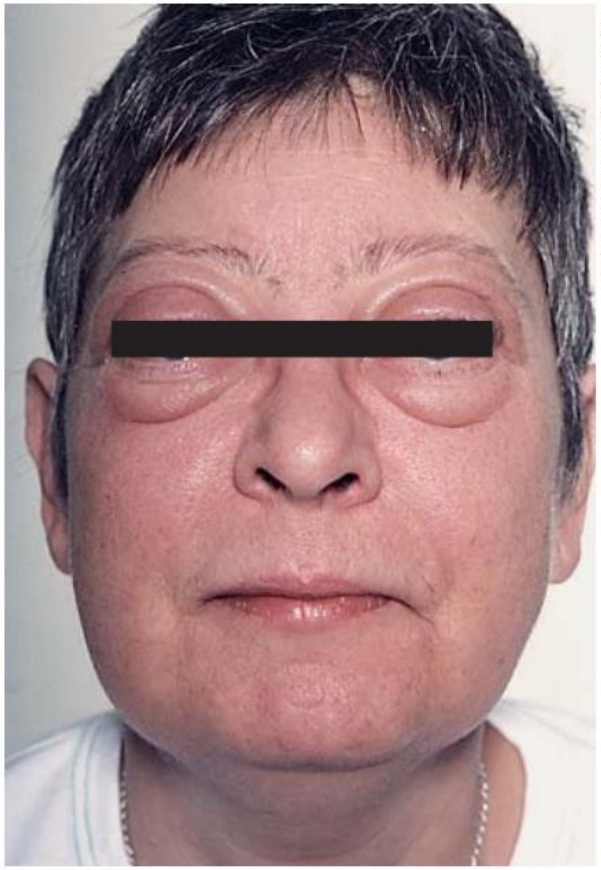

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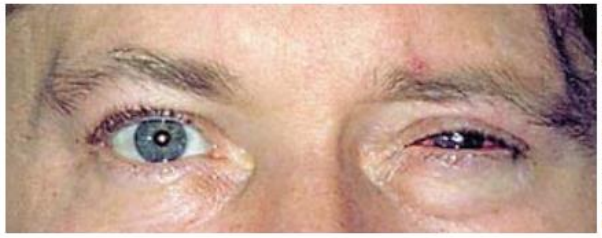

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Fig. 8. Persistent swelling of the lower lip in a patient with orofacial granulomatosis.

Fig. 9. Edematous urticarial plaques in a patient with hypocomplementemic urticarial vasculitis syndrome.

Fig. 10. Generalized edematous swelling in a patient with Clarkson's disease. Photo credit: Knud Bonnet Yderstræde, MD.

Fig. 11. Characteristic left periorbital edema and partial ptosis, with left conjunctival injection and tear formation during a cluster headache attack. Photo credit: Horton Hovedpineforening (Danish Association for Patients with Cluster Headache), www.hortonforeningen.dk.

Color version available online

Fig. 12. Fluid retention of the face in a patient with idiopathic edema.

Angioedema?

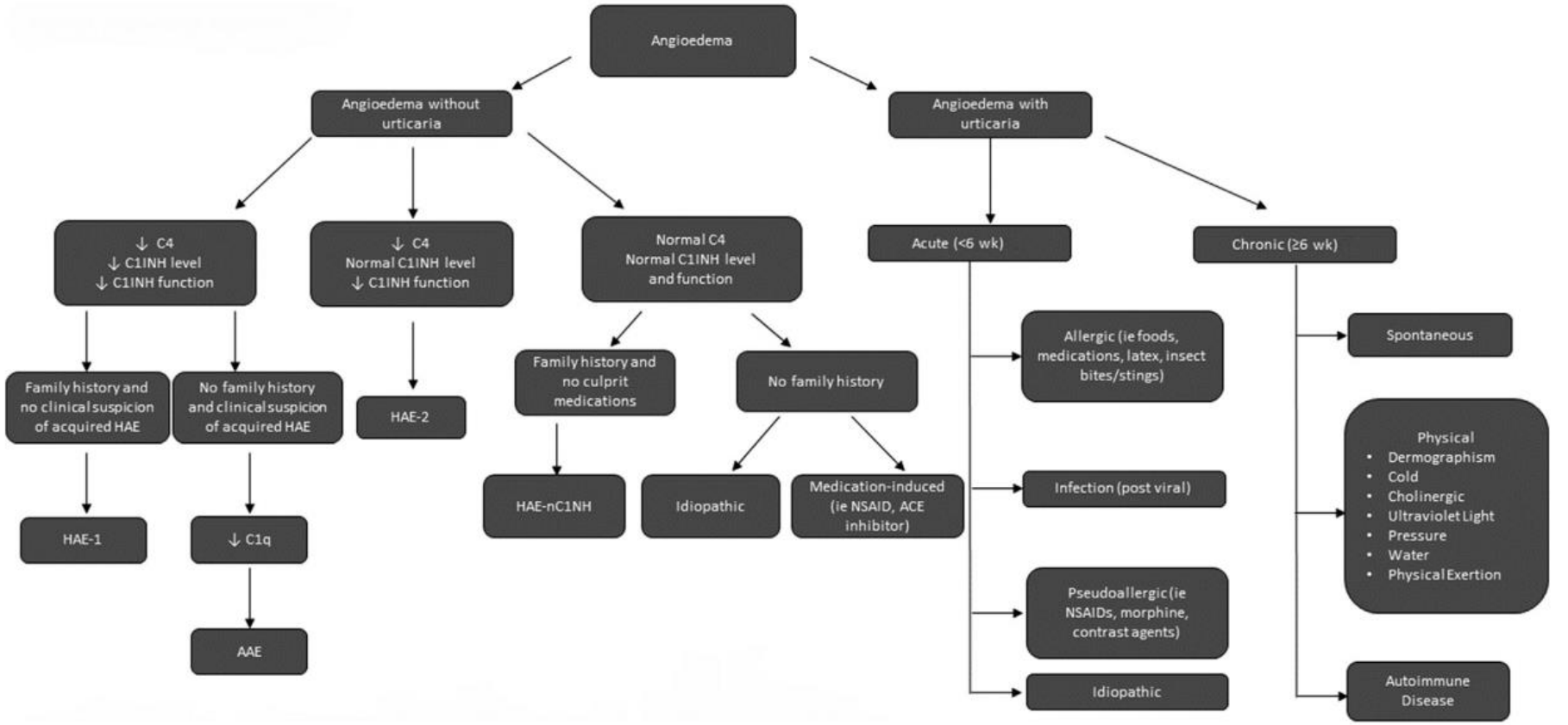

Fig. 5. Angioedema algorithm. AAE, acquired angioedema; C1INH, C1 esterase inhibitor; HAE-nC1NH, hereditary angioedema with normal C1 esterase inhibitor.

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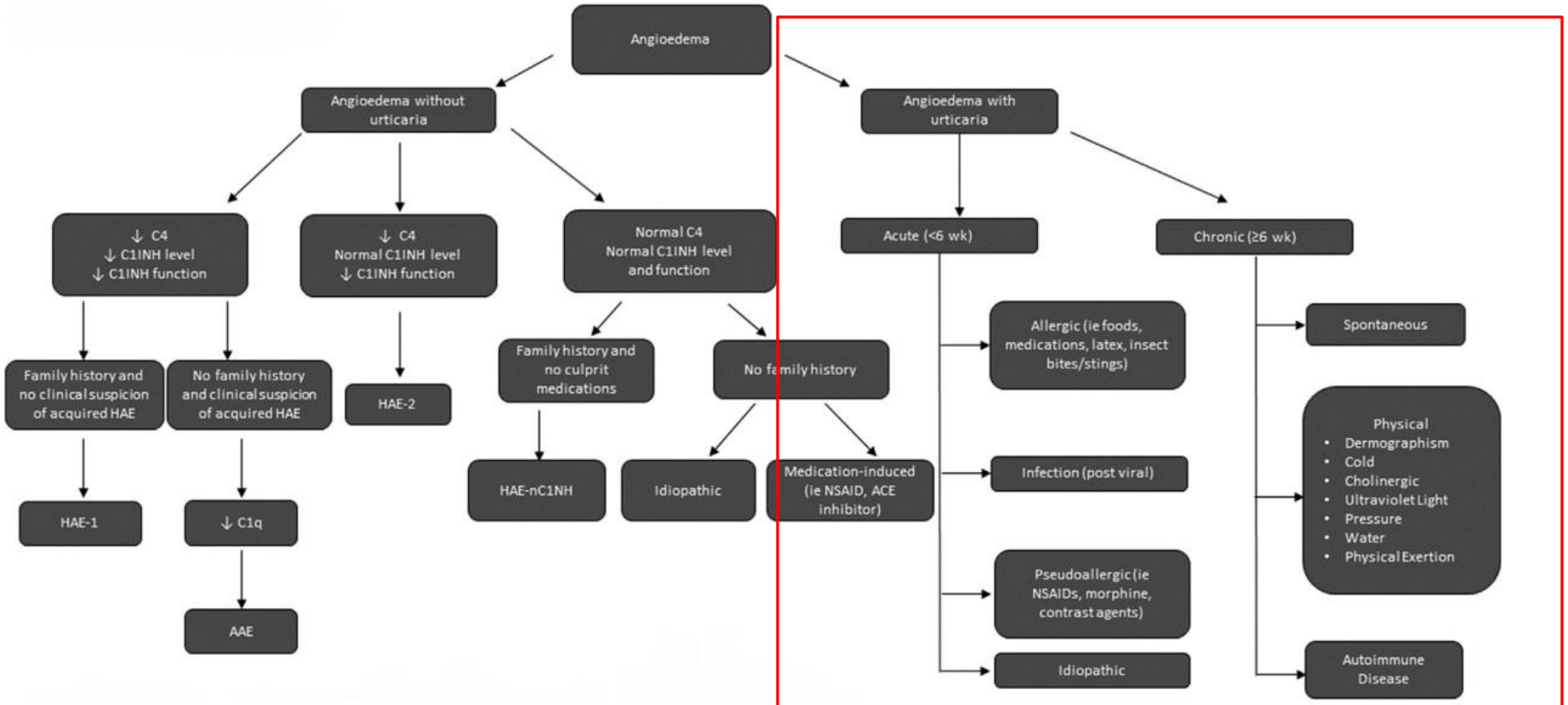
Mast cell pathway



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Case 1

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What would you like to know about the swelling? The rash?

Clinical Differences

Histamine vs bradykinin

- Histamine-mediated
  - Tend to be associated with urticaria
    - 10% of patients only have angioedema
  - Responsive to
    - Antihistamines
    - Steroids
    - Epinephrine
  - Duration is shorter

S1 Table: Mast cell (histamine) versus bradykinin mediated angioedema

Characteristic	Mast cell (histamine)	Bradykinin
Rate of onset	Minutes	Hours
Duration of swelling	24 – <48 hours	>48 hours
Urticaria	+	–
Pruritis	+	–
Pain/burning	–	May be present
Response to antihistamine	+	–
Response to corticosteroids	+	–

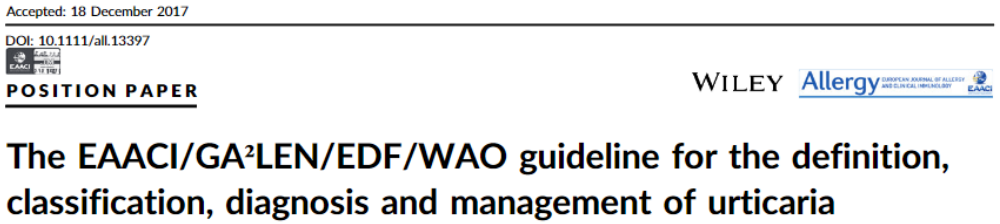
+ = Present, – = Not commonly present

Busse, P. J., & Christiansen, S. C. (2020). Hereditary Angioedema. The New England Journal of Medicine, 382, 1136–1148.

Approach to Urticaria

Most pertinent details on history:

1. Is this hives?
   - Onset of disease
   - Characteristic of rash, including pattern of distribution
2. Acute or chronic?
   - Duration of symptoms (? >6 weeks)
3. Is there associated angioedema?
4. Identified triggers?
   - Acute: food, medications, venom, latex, infection
   - Chronic: infections, stress, NSAIDs, alcohol, physical triggers
5. Red flag features of systemic disorders?
   - Painful, scarring, prolonged rash?
   - Associated symptoms – fever, joint pain, family history, constitutional symptoms
6. Prior treatments?


Accepted: 18 December 2017
DOI: 10.1111/all.13397
POSITION PAPER
WILEY Allergy

The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria

Adapted from Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, B., Bernstein, J. A., Bindslev-Jensen, C., Brzoza, Z., Buense Bedrikow, R., Canonica, G. W., Church, M. K., Craig, T., Danilycheva, I. V., Dressler, C., Ensina, L. F., Giménez-Arnau, A., Godse, K., Gonçalo, M., ... Maurer, M. (2018). The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy: European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.13397

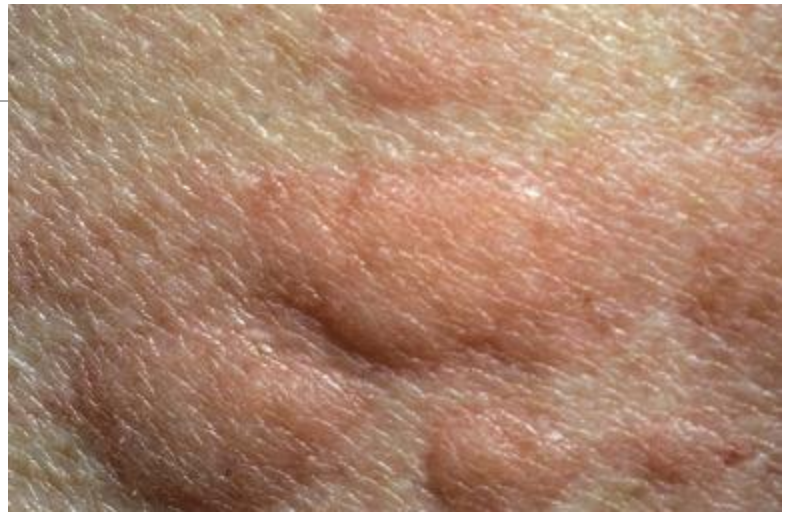
Urticaria

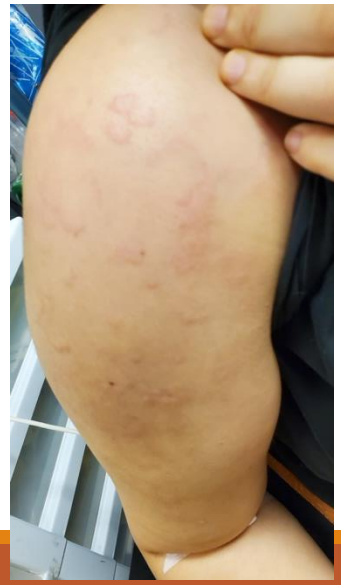
What makes a rash urticaria?

Clinical Features

Hives:

- Plaque of variable size
- Sometimes **central paleness** and **surrounding erythema**
- **Pruritic**, not painful
- **Transient** – usually 30 min to 24 hrs, <48 hrs
- Non-scarring
- May appear flat if blunted by antihistamines
- Affects 15-20% of people in their lifetime!





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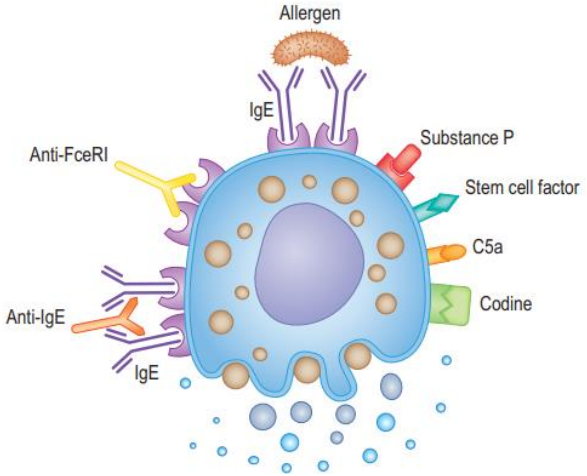
Pathophysiology

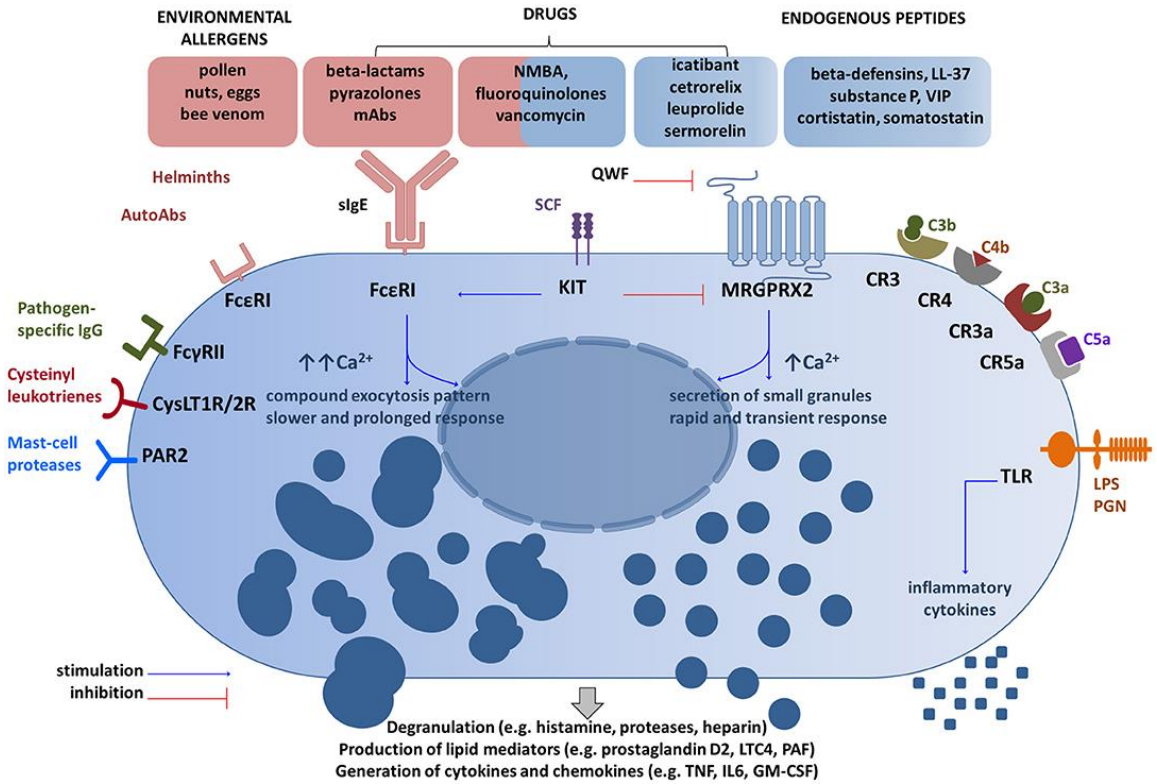
Mast cell pathway – driver for hives and most angioedema

Degranulation of mast cells, basophils

Release of vasoactive mediators

- **Histamine**
- Lipid mediators (PGD_2, LTC_4, LTD_4)
- Cytokines





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Porebski et al. Front. Immunol 2018
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Systemic Conditions – Mimickers of Urticaria

Anaphylaxis

Urticarial vasculitis

Cutaneous mastocytosis

Autoinflammatory conditions

- Acquired
  - Schnitzler's syndrome
- Congenital
  - CAPS

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (eg, HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches), that is familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) or neonatal-onset multisystem inflammatory disease (NOMID).
- Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
- Gleich's syndrome (episodic angioedema with eosinophilia)
- Well's syndrome (granulomatous dermatitis with eosinophilia/eosinophilic cellulitis)
- Bullous pemphigoid (prebullous stage)

Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, B., Bernstein, J. A., Bindslev-Jensen, C., Brzoza, Z., Buense Bedrikow, R., Canonica, G. W., Church, M. K., Craig, T., Danilycheva, I. V., Dressler, C., Ensina, L. F., Giménez-Arnau, A., Godse, K., Gonçalo, M., … Maurer, M. (2018). The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy: European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.13397

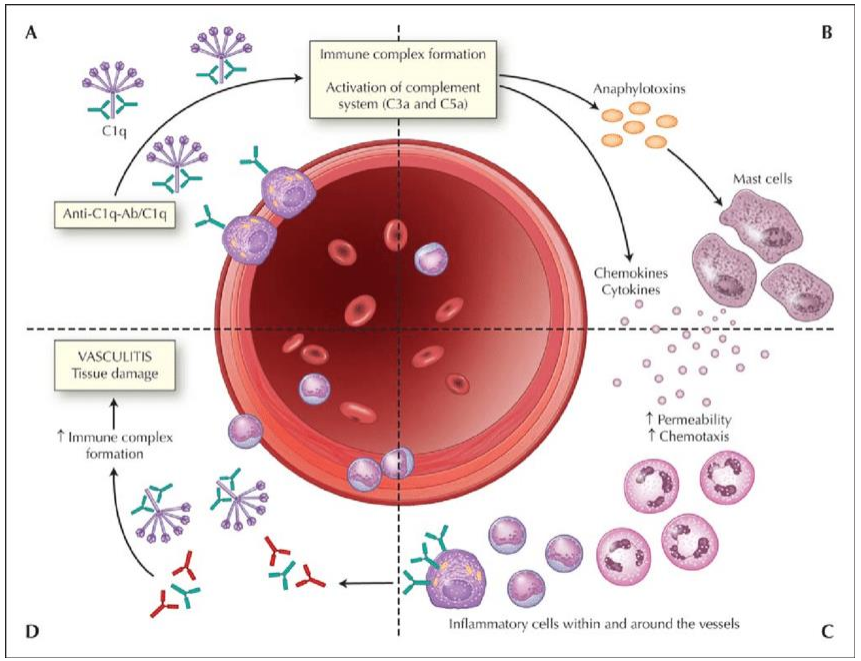
Urticarial Vasculitis

Immune complex deposition

Clinical features:

- Lasts longer than urticaria (>24 hours)
- Residual tissue damage and scarring
- May present with pain rather than itch
- May have associated purpura

Investigate for potential secondary cause



Cutaneous Mastocytosis

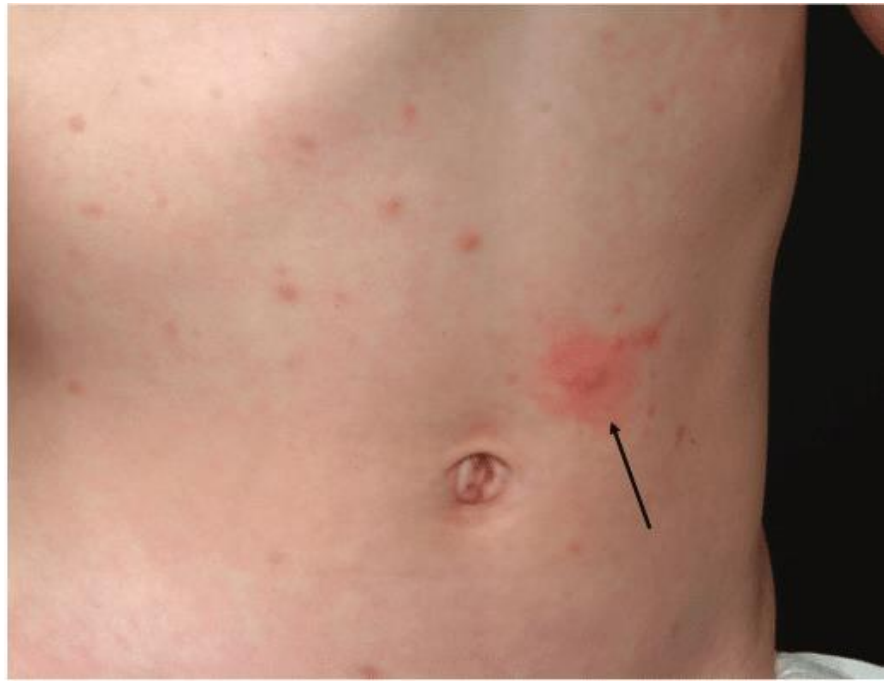
Excessive mast cell accumulation limited to the skin

Urticaria pigmentosa

Diffuse cutaneous mastocytosis

Mastocytoma

Screen with serum tryptase



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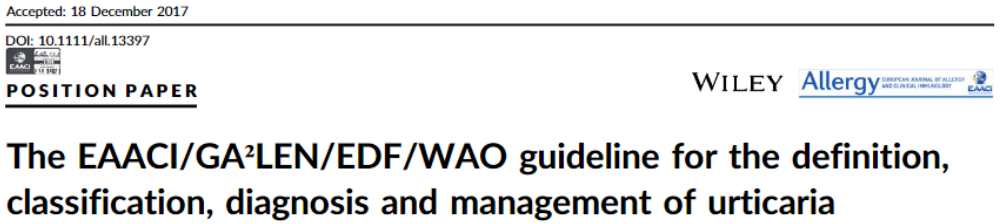
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Common Causes of Urticaria

Acute (<6 weeks)

- Allergy
- Infection
- Direct mast cell degranulation
- Idiopathic

Chronic (>6 weeks)

- Chronic spontaneous urticaria
- Chronic inducible urticaria

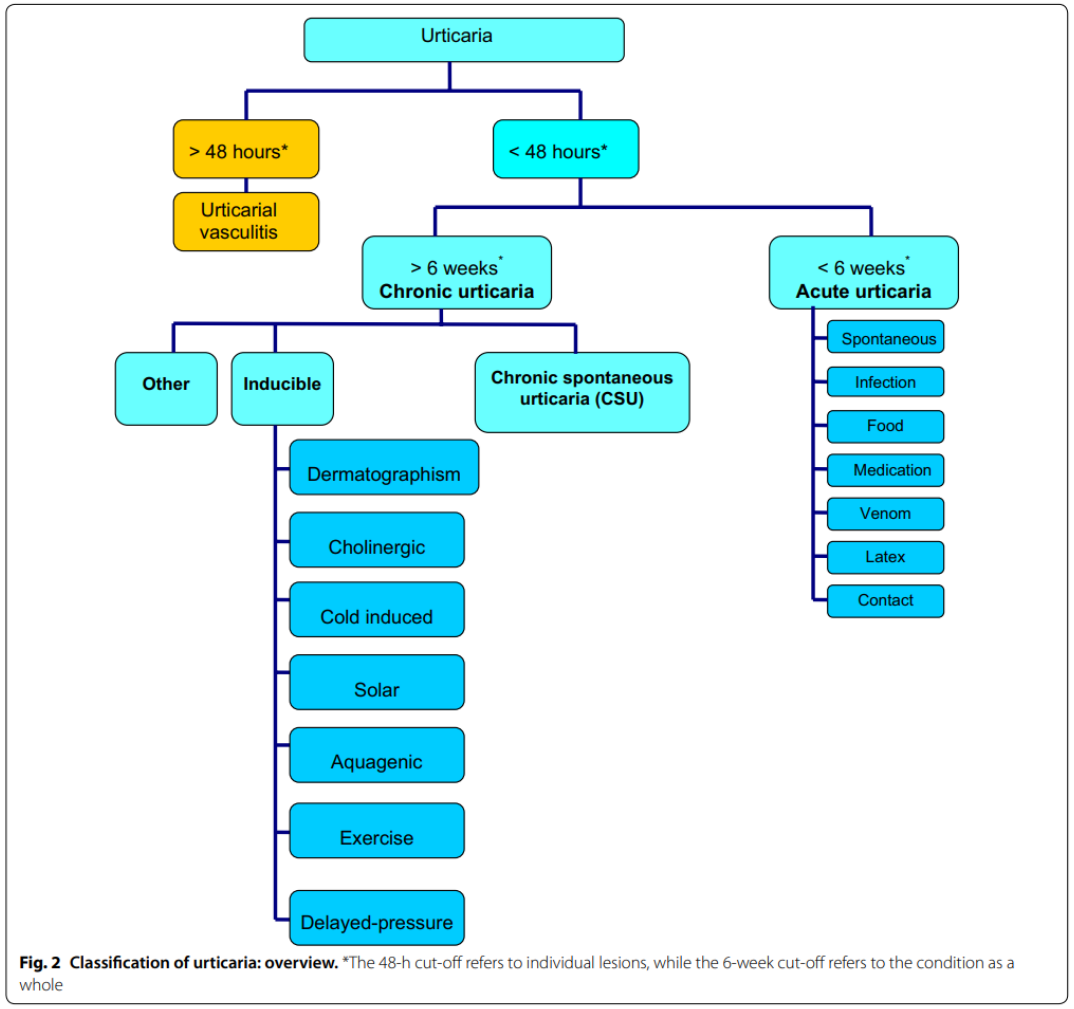

Fig. 2 Classification of urticaria: overview. *The 48-h cut-off refers to individual lesions, while the 6-week cut-off refers to the condition as a whole

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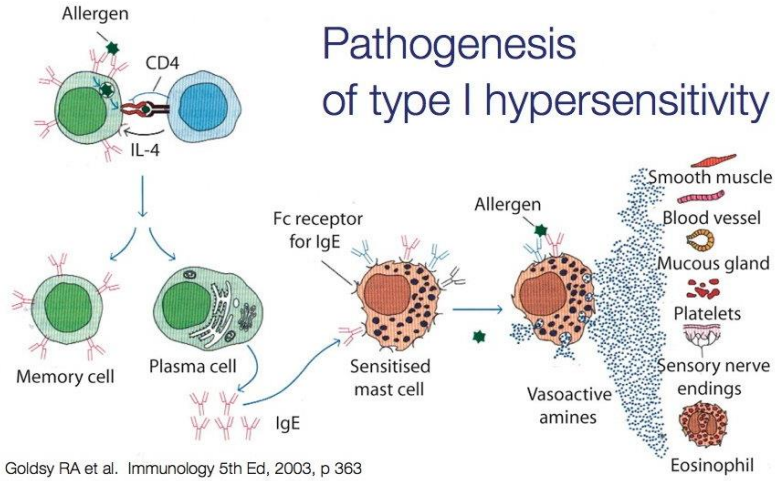
Acute Urticaria - Allergies

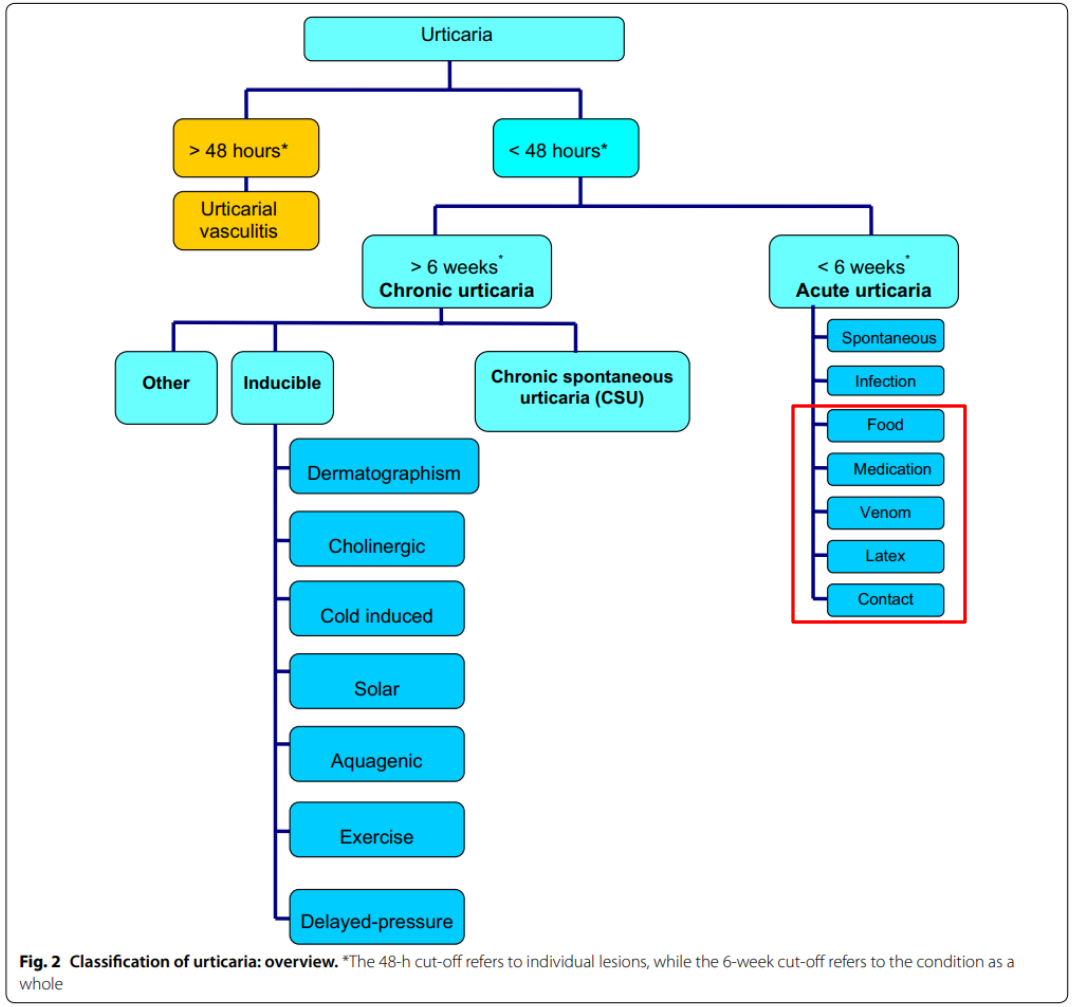
IgE-mediated mast cell degranulation

Clear timing correlation with potential trigger – within 2 hours

Screen for features of **anaphylaxis**



Goldsy RA et al. Immunology 5th Ed, 2003, p 363



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Acute Urticaria - Allergies

Food allergy

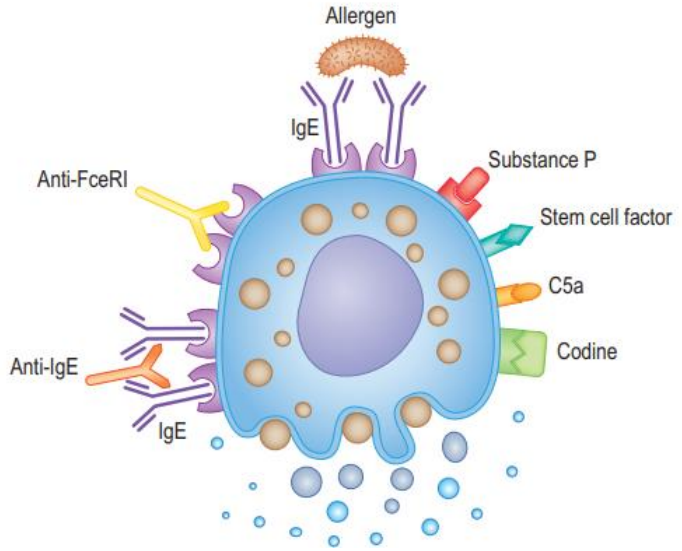
- 11 priority food allergens
  - Egg, Cow's milk, Wheat, Sesame, Soy, Peanut, Tree nuts, Fish, Shellfish, Mustard

Potential delayed symptoms

- Red meat allergy
  - Carbohydrate rather than protein
  - Alpha-gal moiety

Food allergen type	Number of patients reporting one or more foods from a specific food group caused the allergic reaction (%)	Foods[a] from each group reported as being responsible for the allergic reaction, n	Allergist ranked as "Possible or probable" IgE-mediated allergy, n (% of total reported)
Legumes	13 (19.1)	Green pea: n = 13	Green pea: n = 9 (69.2)
		Lentil: n = 7	Lentil: n = 4 (57.1)
		Chickpeas: n = 3	Chickpeas: n = 3 (100)
		Split peas: n = 1	Split peas: n = 1 (100)
		Lupin: n = 1	Lupin: n = 1 (100)
Seeds	15 (22.1)	Coconut: n = 7	Coconut: n = 3 (42.9)
		Pumpkin seed: n = 4	Pumpkin seed: n = 1 (25.0)
		Chia seeds: n = 3	Chia seeds: n = 1 (33.3)
		Poppy seed: n = 2	Poppy seed: n = 0 (0.00)
		Flax: n = 2	Flax: n = 1 (50.0)
		Sunflower: n = 1	Sunflower: n = 1 (100)
		Hemp seeds: n = 1	Hemp seeds: n = 1 (100)
Fruits & vegetables	40 (58.8)	Corn: n = 9	Corn: n = 1 (11.1)
		Pineapple: n = 6	Pineapple: n = 5 (83.3)
		Mango: n = 5	Mango: n = 1 (20.0)

Acute Urticaria - Allergies

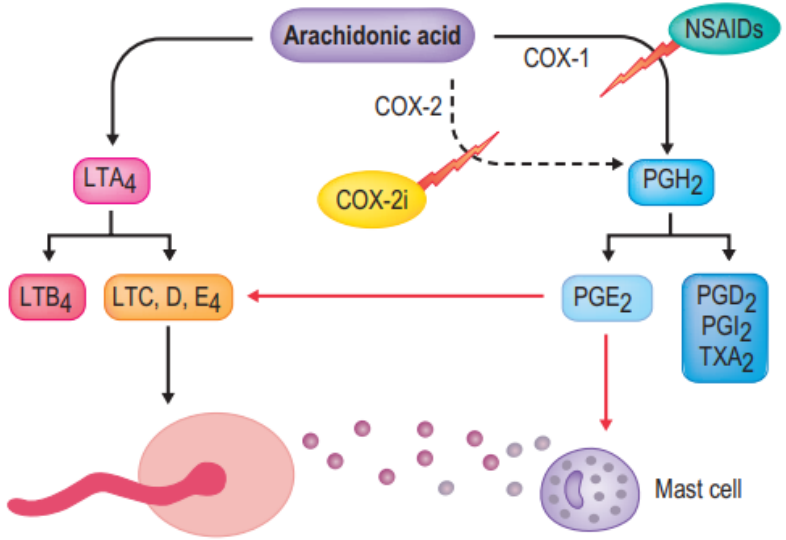


Medication allergy

- Most commonly antibiotics, NSAIDs

NSAID

- Overproduction of LTC, D, E_4
- Reduced effect of PGE_2 on inhibition of mast cell degranulation



Direct mast cell degranulation

- Radiocontrast media
- Paralysis agents
- Opioids
- Vancomycin – “Red man syndrome”

Clive E.H. Grattan, Elena Borzova, 42 - Urticaria, Angioedema, and Anaphylaxis, Editor(s): Robert R. Rich, Thomas A. Fleisher, William T. Shearer, Harry W. Schroeder, Anthony J. Frew, Cornelia M. Weyand, Clinical Immunology (Fifth Edition), Elsevier, 2019, Pages 585-600.e1, ISBN 9780702068966, https://doi.org/10.1016/B978-0-7020-6896-6.00042-9.

Acute Urticaria - Allergies

Insect sting allergy – hymenoptera

- Honeybee
- Yellowjacket
- Bald-faced hornet
- Yellow hornet
- Paper wasp
- Fire ant

Acute Urticaria - Infection

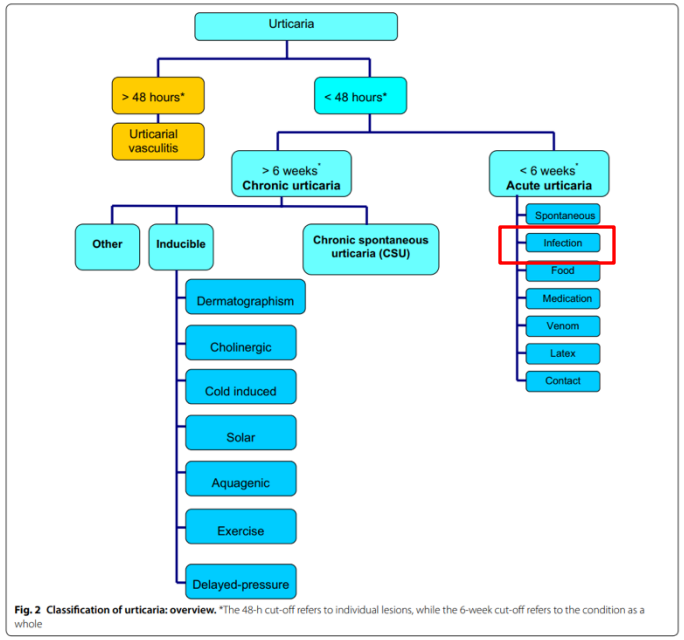


Fig. 2 Classification of urticaria: overview. *The 48-h cut-off refers to individual lesions, while the 6-week cut-off refers to the condition as a whole

Post-infectious

- Up to 80% of pediatric presentations
  - Based on a prospective study of ED visits with urticaria
- Post-viral
  - Reported: HSV-1, HSV-2, HHV-6, EBV, CMV, parvovirus B19, norovirus, HAV, HCV
- Bacterial
  - Reported: Streptococcus, staphylococcus, mycoplasma, salmonella, brucella, borrelia, chlamydia, yersinia

Association between urticaria and virus infections: A systematic review

Egidio Imbalzano, M.D.,[1] Marco Casciaro, M.D.,[2] Sebastiano Quartuccio, M.D.,[1] Paola L. Minciullo, M.D., Ph.D.,[2] Antonio Cascio, M.D., Ph.D.,[3] Gioacchino Calapai, M.D.,[1,4] and Sebastiano Gangemi, M.D., Ph.D.[2]

Urticaria and bacterial infections

Paola L. Minciullo, M.D., Ph.D.,[1] Antonio Cascio, M.D., Ph.D.,[2] Giuseppina Barberi, Ph.D.,[2] and Sebastiano Gangemi, M.D., Ph.D.[1,3]

Association between urticaria and nematode infections

Paola L. Minciullo, M.D., Ph.D.,[1] Antonio Cascio, M.D., Ph.D.,[2] and Sebastiano Gangemi, M.D., Ph.D.[1,3]

Acute Urticaria - Investigations

EAACI/GA²LEN/EuroGuiDerm/APAACI guideline (2022)

TABLE 8 Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme[a] (based on history) – For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[b]
	CSU	Differential blood count, ESR	Avoidance of suspected triggers (eg, drugs);

[b]Unless strongly suggested by patient history, for example, allergy.

Consider allergy testing if type I reaction suspected

Treatment? – stay tuned

Chronic Spontaneous Urticaria

Epidemiology:

- Prevalence up to 5%
- F > M (2:1)
- Typical age of onset: 30-50

TABLE 4 Recommended classification of chronic urticaria

Chronic urticaria subtypes	
Chronic Spontaneous Urticaria (CSU)	**Inducible Urticaria**
Spontaneous appearance of wheals, angioedema or both for > 6 weeks due to known[a] or unknown causes	Symptomatic dermographism[b] Cold urticaria[c] Delayed pressure urticaria[d] Solar urticaria Heat urticaria[e] Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

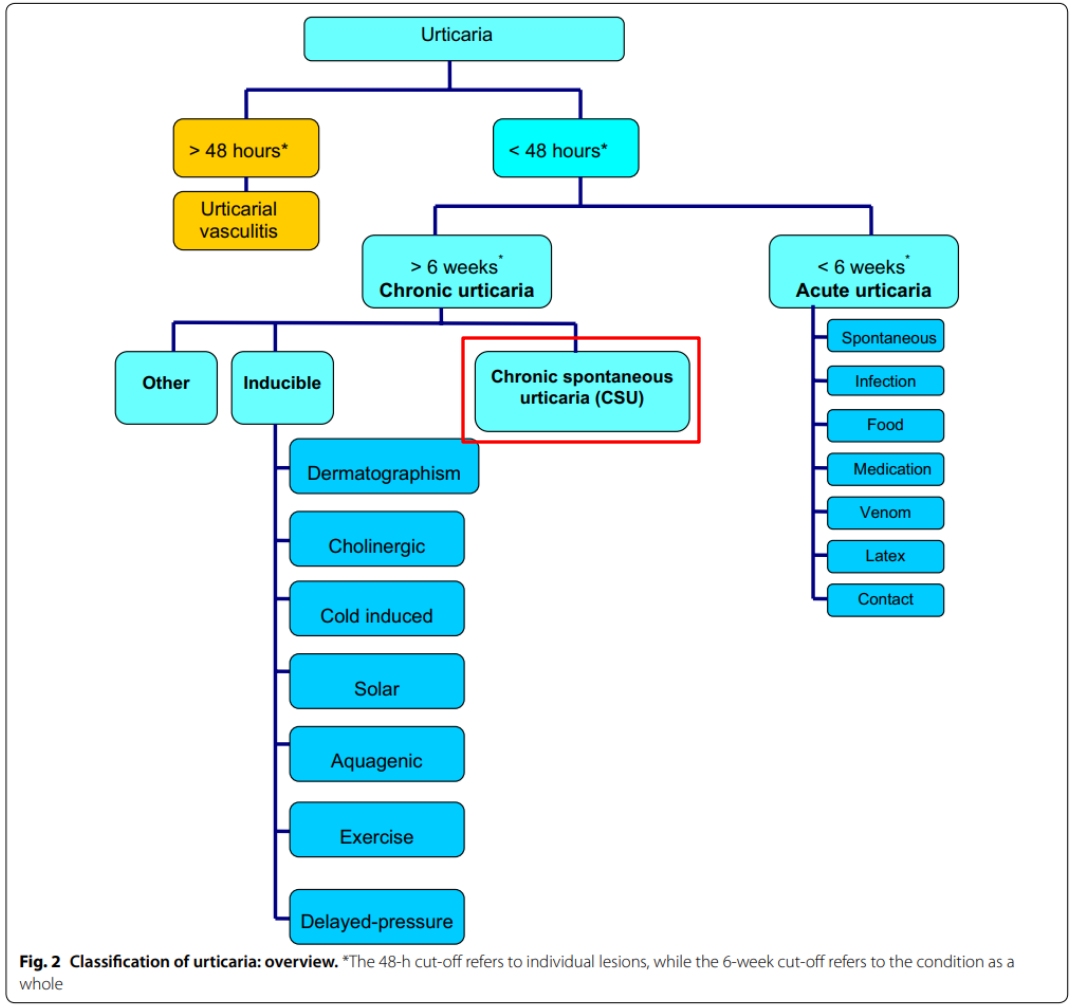


Fig. 2 Classification of urticaria: overview. *The 48-h cut-off refers to individual lesions, while the 6-week cut-off refers to the condition as a whole

Kanani, A., Betschel, S. D., & Warrington, R. (2018). Urticaria and angioedema. Allergy, Asthma and Clinical Immunology. https://doi.org/10.1186/s13223-018-0288-7

Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, B., Bernstein, J. A., Bindslev-Jensen, C., Brzoza, Z., Buense Bedrikow, R., Canonica, G. W., Church, M. K., Craig, T., Danilycheva, I. V., Dressler, C., Ensina, L. F., Giménez-Arnau, A., Godse, K., Gonçalo, M., … Maurer, M. (2018). The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy: European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.13397

Chronic Spontaneous Urticaria

Prognosis?

- Resolution in 30-50% of patients in 1 year
- Mean duration 48 months (local data)
- Does not progress to anaphylaxis

Table II. Percentages of patients free of symptoms after 1 year

Idiopathic, all patients	47.4% (37/78)
Urticaria only	38.5% (10/26)
Angioedema only	20.0% (2/10)
Both urticaria and angioedema	59.5% (25/42)
Physical and idiopathic urticaria	20.8% (5/24)
Physical urticarias	16.4% (12/73)

Table 2 Duration of CSU in patients with resolved disease and subgroups

Duration of CSU	Median Duration of CSU (months)	Mean Duration of CSU (months)	6 weeks–23 months	24–47 months	48–71 months	72–95 months	96–119 months	120 months and greater
All Patients with Resolved CSU $n = 56$ (%)	48	61 ± 56	17 (30)	9 (16)	11 (20)	5 (9)	5 (9)	9 (16)

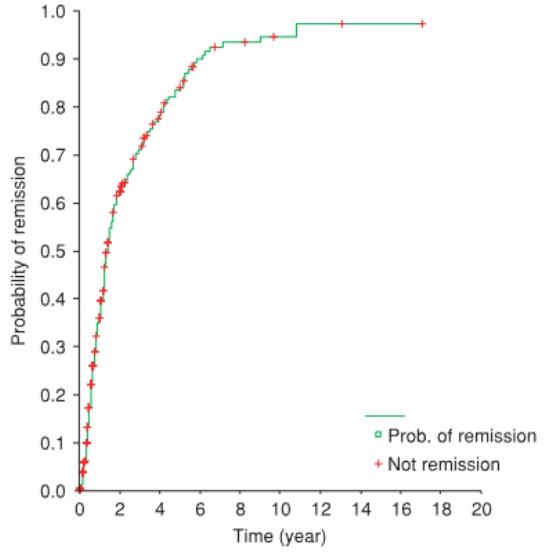


Figure 1. A Kaplan–Meier curve demonstrating duration of the disease in patients with chronic idiopathic urticaria ($n = 337$). After 1 year from the onset of the symptoms, 34.5% of patients were free of symptoms.

KULTHANAN, K., JIAMTON, S., THUMPIMUKVATANA, N., & PINKAEW, S. (2007). Chronic idiopathic urticaria: prevalence and clinical course. The Journal of Dermatology, 34(5), 294–301. https://doi.org/10.1111/j.1346-8138.2007.00276.x

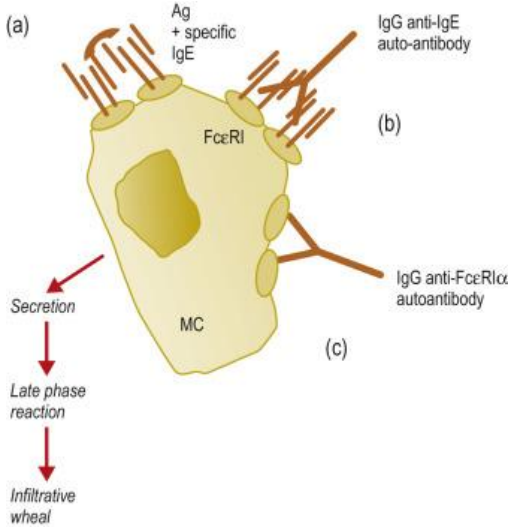
Kozel, M. M. A., Mekkes, J. R., Bossuyt, P. M. M., & Bos, J. D. (2001). Natural course of physical and chronic urticaria and angioedema in 220 patients. Journal of the American Academy of Dermatology, 45(3), 387–391. https://doi.org/10.1067/mjd.2001.116217

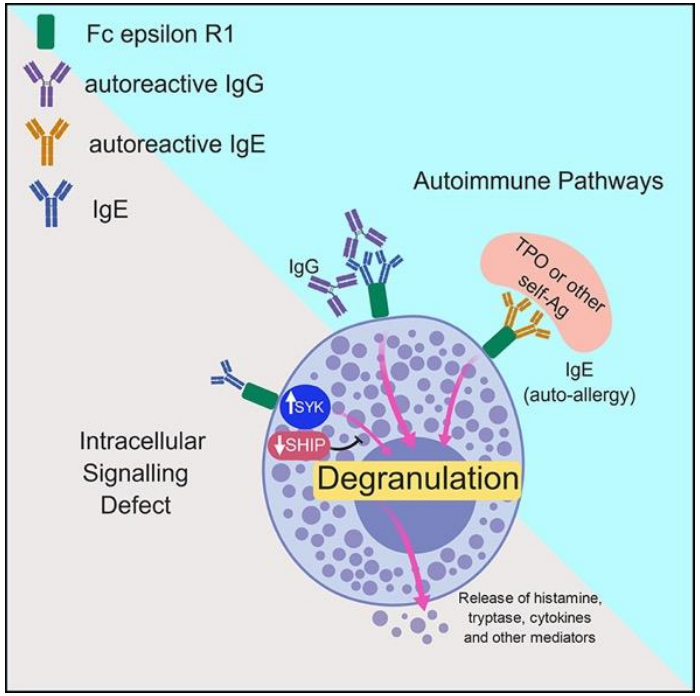
Stepaniuk, P., Kan, M., & Kanani, A. (2020). Natural history, prognostic factors and patient perceived response to treatment in chronic spontaneous urticaria. Allergy, Asthma & Clinical Immunology, 16(1), 63. https://doi.org/10.1186/s13223-020-00459-5

Chronic Spontaneous Urticaria

Pathophysiology:

- Unclear
- Up to 50% with self mast cell degranulating antibodies





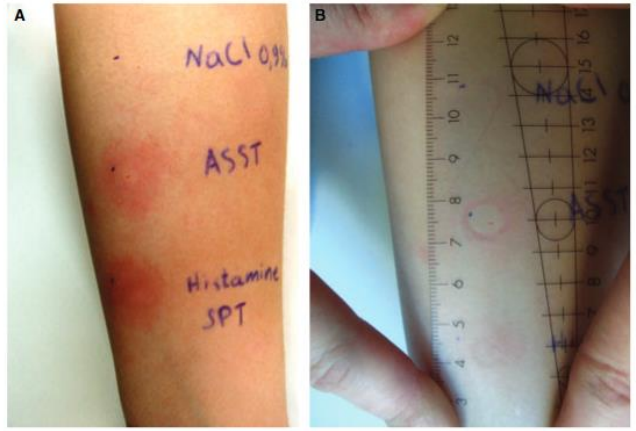


Figure 2. (A) A positive autologous serum skin test (ASST) at 30 min. The figure shows a negative control (NaCI 0.9%, normal saline), a positive weal response to autologous serum with a mean diameter of 7.5 mm and a fading positive histamine skin prick test response (positive control). (B) After pressure with a transparent ruler, the erythema blanches and the oedema within the skin test site (weal reaction) separates clearly and becomes much easier to define.

A Wesley Burks. (2019). Middleton's Allergy Principles and Practice.

B Confino-Cohen, R., Chodick, G., Shalev, V., Leshno, M., Kimhi, O., & Goldberg, A. (2012). Chronic urticaria and autoimmunity: Associations found in a large population study. Journal of Allergy and Clinical Immunology. https://doi.org/10.1016/j.jaci.2012.01.043

Konstantinou, G. N., Asero, R., Maurer, M., Sabroe, R. A., Schmid-Grendelmeier, P., & Grattan, C. E. H. (2009). EAACI/GA 2 LEN task force consensus report: the autologous serum skin test in urticaria. Allergy, 64(9), 1256–1268. https://doi.org/10.1111/j.1398-9995.2009.02132.x

Chronic Spontaneous Urticaria

Spontaneous… but potential triggers?

- NSAIDs
- Alcohol
- Opiates
- Stress
- Menstruation

Patient reported provoking factors	
Dermatographia	34 (47)
Stress	27 (38)
Heat	25 (35)
Cold	10 (14)
Foods	8 (11)
NSAIDs	8 (11)
Exercise	7 (10)
Alcohol	5 (7)
Sunlight	2 (3)

Stepaniuk, P., Kan, M., & Kanani, A. (2020). Natural history, prognostic factors and patient perceived response to treatmentin chronic spontaneous urticaria. Allergy, Asthma & Clinical Immunology, 16(1), 63. https://doi.org/10.1186/s13223-020-00459-5

Exacerbation of CSU +/- Angioedema

Pathophysiology?

- Presumed secondary to COX-1 inhibition

TABLE II. NSAID challenge tests without antihistamines

NSAID challenges without anti-H1	Total no. of NSAID challenges: 204 (100%)	(+) challenges: 141 (69.1%)	(−) challenges: 63 (30.9%)
Strong COX1-inh (n 115)			
Acetylsalicylic acid (1000 mg)	51	49	2
Ibuprofen (1000 mg)	34	34	0
Diclofenac (150 mg)	30	30	0
Weak COX1-inh (n = 68)			
Acetaminophen (1000 mg)	17	4	13
Meloxicam (15 mg)	21	3	18
Nimesulide (175 mg)	30	20	10
Selective COX2-inh (n = 21)			
Celecoxib (300 mg)	15	1	14
Etoricoxib (105 mg)	6	0	6

The challenge tests are grouped according to the result (columns) and the used NSAID (rows).

Sánchez J, Diez S, Cardona R. Clinical Control of CSU with Antihistamines Allows for Tolerance of NSAID-Exacerbated Cutaneous Disease. J Allergy Clin Immunol Pract. 2020;8(10):3577-3583.e1. doi:10.1016/j.jaip.2020.06.057

Chronic Spontaneous Urticaria

Disease associations

- Autoimmunity
  - Confino-Cohen et al 2009 (n = 12778)

TABLE I. Autoimmune diseases in patients with CU and control subjects

	Total population (n = 12,778 patients with CU and 10,714 control subjects)			Female subjects (n = 8,472 patients with CU and 9,188 control subjects)			Male subjects (n = 4,306 patients with CU and 1,526 control subjects)		
Disease	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Hypothyroidism	17.338	13.51-22.2	<.0005	23.07	17.80-29.91	<.0005	7.57	3.33-17.21	<.0005
Hyperthyroidism	28.81	15.40-54.25	<.0005	34.98	18.00-67.99	<.0005	19.73	2.72-142.69	<.0005
RA	13.25	7.39-23.76	<.0005	19.88	10.15-38.92	<.0005	2.96	0.89-9.83	.06
Type I diabetes mellitus	7.703	4.78-12.65	<.0005	12.92	6.53-25.53	<.0005	2.34	1.15-4.73	.01
Sjögren syndrome	15.17	5.54-14.54	<.0005	23.30	7.31-74.20	<.0005	2.83	0.35-22.71	.30
Celiac disease	26.96	6.6-110.17	<.0005	57.83	7.99-418.29	<.0005	3.90	0.50-30.27	.16
SLE	14.59	4.56-46.73	<.0005	26.71	6.49-109.90	<.0005	1.06	0.11-10.22	.96

TABLE II. Timing of first diagnosis of autoimmune disease in relation to diagnosis of CU

	Before diagnosis of CU (%)			After diagnosis of CU (%)		
Disease	**Women**	**Men**	**Total**	**Women**	**Men**	**Total**
Hypothyroidism	218/1132 (19.3)	22/125 (17.6)	240/1257 (19.1)	914/1132 (80.7)	103/125 (82.4)	1017/1132 (80.9)
Hyperthyroidism	49/281 (17.4)	10/55 (18.2)	59/336 (17.6)	232/281 (82.6)	45/55 (81.8)	277/336 (82.4)
RA	28/162 (17.3)	4/25 (16.0)	32/187 (17.1)	134/162 (82.7)	21/25 (84.0)	155/187 (82.9)
Type I diabetes mellitus	18/106 (17.0)	7/59 (11.9)	25/165 (15.2)	88/106 (83.0)	52/59 (88.1)	140/165 (84.8)
Sjögren syndrome	13/64 (20.3)	3/8 (37.5)	16/72 (22.2)	51/64 (79.7)	5/8 (62.5)	56/72 (77.8)
Celiac disease	6/53 (11.3)	5/11 (45.5)	11/64 (17.2)	47/53 (88.7)	6/11 (54.5)	53/64 (82.8)
SLE	8/49 (16.3)	0 (0.0)	8/52 (15.4)	41/49 (83.7)	3/3 (100)	44/52 (84.6)

. B Confino-Cohen, R., Chodick, G., Shalev, V., Leshno, M., Kimhi, O., & Goldberg, A. (2012). Chronic urticaria and autoimmunity: Associations found in a large population study. Journal of Allergy and Clinical Immunology https://doi.org/10.1016/j.jaci.2012.01.043

Chronic Spontaneous Urticaria

Disease associations

- Malignancy? Conflicting evidence
  - Lindelof et al 1990
    - N = 1115 Swedish patients, followed for 8.2 years
    - No increase in malignancy
  - Kozel et al. 2003
    - N = 6462 patients
    - No association
  - Chen et al. 2012
    - N = 12720 Taiwanese patients
    - Increased rate of all malignancy

Table 4. Standard Incidence Ratios (SIRs) of Specific Types of Hematologic Malignant Tumors in Chronic Urticaria[a]

Type	No. Observed	No. Expected	SIR (95% CI)
Total	**58**	**14**	4.1 (3.1-5.4)
Non-Hodgkin lymphoma	35	8	4.4 (3.0-6.1)
Hodgkin lymphoma	1	0	. . .
Leukemia	22	6	3.7 (2.3-5.6)

[a] Based on the 2003 Cancer Registry Report of Taiwan.

Table 5. Standard Incidence Ratios (SIRs) of Nonhematologic Cancers in Chronic Urticaria[a]

Cancer Type	No. Observed	No. Expected	SIR (95% CI)
Total	**646**	**310[b]**	2.1 (1.9-2.3)
Oral cavity	**49**	**24**	2.0 (1.5-2.7)
Tongue, gingiva	25	11	2.3 (1.5-3.4)
Oropharynx, hypopharynx, and others	8	4	2.0 (0.9-3.9)
Larynx	4	3	1.3 (0.4-3.4)
Nasopharynx	10	5	2.0 (1.0-3.7)
Nose, sinus, and ear	2	1	2.0 (0.2-7.2)
Hepatogastroenterologic system	**303**	**135**	2.2 (2.0-2.5)
Esophagus	19	7	2.7 (1.6-4.2)
Stomach	42	20	2.1 (1.5-2.8)
Small intestine	1	2	0.5 (0.0-2.8)
Colorectum, cecum, and anus	78	46	1.7 (1.3-2.1)
Liver and gallbladder	146	53	2.8 (2.3-3.2)
Pancreas	12	7	1.7 (0.9-3.0)
Retroperitoneum and others	5	1	5.0 (1.6-11.7)
Lungs and mediastinum	**105**	**46**	2.3 (1.9-2.8)
Lungs and trachea	102	45	2.3 (1.8-2.8)
Mediastinum including heart, thymus	3	1	3.0 (0.6-8.8)
Skin	**14**	**10**	1.4 (0.8-2.3)
Melanoma	1	1	1.0 (0.0-5.6)
Nonmelanoma	13	9	1.4 (0.8-2.5)
Female genitalia	**33**	**16**	2.2 (1.5-3.1)
Uterus	5	3	1.7 (0.5-3.9)
Cervix including ovary	24	12	2.0 (1.3-3.0)
Vulva, placenta, and others	4	1	4.0 (1.1-10.2)
Female breast	**32**	**19**	1.7 (1.2-2.4)
Male genitalia	**29**	**17**	1.7 (1.1-2.4)
Prostate	26	16	1.6 (1.1-2.4)
Testis, penis, and others	3	1	3.0 (0.6-8.8)
Genitourinary system	**45**	**20**	2.3 (1.6-3.0)
Bladder	15	11	1.4 (0.8-2.2)
Kidney, urinary system, and others	30	9	3.3 (2.2-4.8)
Others	**28**	**8**	3.1 (2.1-4.5)
Brain	10	2	5.0 (2.4-9.2)
Other neural systems	1	0	. . .
Bone, joint, and soft tissue	4	2	2.0 (0.5-5.1)
Thyroid gland	11	4	2.8 (1.4-4.9)
Endocrine system other than thyroid	2	0	. . .
Ill-defined sites	**2**	0	. . .
Unknown origin	**6**	6	1.0 (0.4-2.2)

[a] Based on the 2003 Cancer Registry Report of Taiwan. All data were rounded to a whole number.
[b] The sum may not equal to the overall expected number because of the different observation times in each stratification.

Chen, Y.-J. (2012). Cancer Risk in Patients With Chronic Urticaria. Archives of Dermatology, 148(1), 103. https://doi.org/10.1001/archdermatol.2011.682

Chronic Spontaneous Urticaria

Infections

- Post-viral
  - Reported: HSV-1, HSV-2, HHV-6, EBV, CMV, parvovirus B19, norovirus, HAV, HCV
- Bacterial
  - Reported: **H. pylori**, Streptococcus, staphylococcus, mycoplasma, salmonella, brucella, borrelia, chlamydia, yersinia

Table 2 Prevalence of different parasites in CSU patients

Type of parasite	*n* of studies	*n* of patients
Giardia spp.	16	>82
Blastocystis hominis	7	>160
Ascaris lumbricoides	7	27
Entamoeba spp.	5	>37
*Anisakis simplex**	2	104
Enterobius vermicularis	3	4
Ancylostoma duodenale	2	3
Taenia spp.	2	3
Toxocara canis	1	33
Trichuris trichiura	1	3
Dientamoeba fragilis	1	1
Necator americanus	1	1

*Unlike other helminths *Anisakis simplex* is thought to cause CSU due to IgE-mediated sensitization to chemicals left by the worms in fish flesh.

Article

COVID-19 Disease Leading to Chronic Spontaneous Urticaria Exacerbation: A Romanian Retrospective Study

Ioana Adriana Muntean [1], Irena Pintea [1,*], Ioana Corina Bocsan [2], Carmen Teodora Dobrican [1,*] and Diana Deleanu [1]

Chronic spontaneous urticaria after COVID-19 primary vaccine series and boosters

Alexis Strahan, MSN,[a,b] Rowanne Ali, BS,[a,c] and Esther E. Freeman, MD, PhD[a,d]
Boston, Massachusetts; Savannah, Georgia; and Washington, DC

Key words: chronic idiopathic urticaria; chronic spontaneous urticaria; COVID-19; cutaneous; dermatology; injection; SARS-CoV-2; skin; vaccine; vaccine reaction.

Research Letter | Allergy

Incidence of Chronic Spontaneous Urticaria Following Receipt of the COVID-19 Vaccine Booster in Switzerland

Olivier Duperrex, MD, MSc; Francesco Tommasini, MD; Yannick D. Muller, MD, PhD

Minciullo, P. L., Cascio, A., Barberi, G., & Gangemi, S. (2014). Urticaria and bacterial infections. In Allergy and Asthma Proceedings. https://doi.org/10.2500/aap.2014.35.3764

Chronic Spontaneous Urticaria

Investigations?

TABLE 8 Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme[a] (based on history) – For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[b]
	CSU	Differential blood count. ESR and/or CRP IgG anti-TPO and total IgE[e]	Avoidance of suspected triggers (eg, drugs); diagnostic tests for (in no preferred order): (i) infectious diseases (eg, *Helicobacter pylori*); (ii) functional autoantibodies (eg, basophil test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, eg, avoidance diet); (v) concomitant CIndU, see below[45];(vi) severe systemic diseases (eg, tryptase); and (vii) other (eg, lesional skin biopsy)

Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, B., Bernstein, J. A., Bindslev-Jensen, C., Brzoza, Z., Buense Bedrikow, R., Canonica, G. W., Church, M. K., Craig, T., Danilycheva, I. V., Dressler, C., Ensina, L. F., Giménez-Arnau, A., Godse, K., Gonçalo, M., … Maurer, M. (2018). The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy: European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.13397

Chronic Inducible Urticaria

Underlying physical trigger of hives

Around 20-30% of chronic urticaria

Pathogenesis typically unclear

TABLE 4 Recommended classification of chronic urticaria

Chronic urticaria subtypes	
Chronic Spontaneous Urticaria (CSU)	**Inducible Urticaria**
Spontaneous appearance of wheals, angioedema or both for > 6 weeks due to known[a] or unknown causes	Symptomatic dermographism[b] Cold urticaria[c] Delayed pressure urticaria[d] Solar urticaria Heat urticaria[e] Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

Table 2 Definition, frequency, and duration of CIndUs

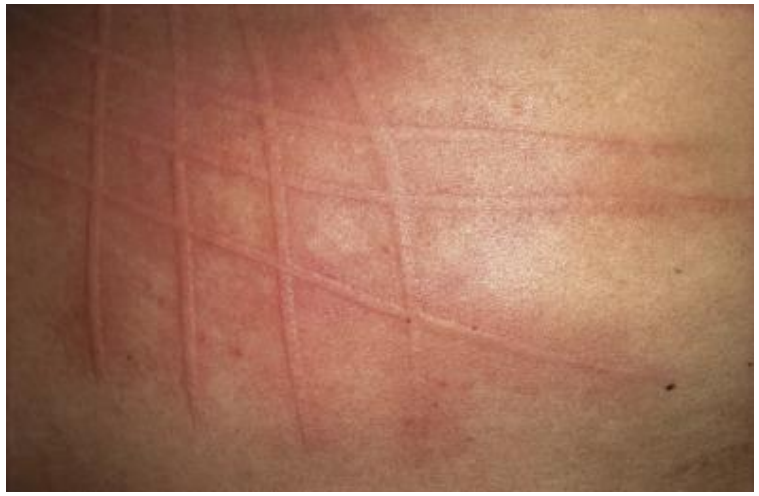
	Definition	Frequency*	Duration*
Symptomatic dermographism	Itching and/or burning skin and the development of strip-shaped wheals due to shear force acting on the skin	1–5% in the general population (10, 139–141)	6.5 years with a great variance (142–144)
Cold Urticaria	Itchy wheals or angioedema after cold exposure of the skin	Up to one-third of all PhysU cases (145)	4.8–7.9 years (27, 28, 32)
Heat Urticaria	Itchy wheals after heat exposure of the skin	Very rare, no data available	Very rare, no data available
Delayed Pressure Urticaria	Erythematous skin swelling after the application of sustained pressure	37% of patients with CSU (64) but rare as a primary inducible urticaria	6–9 years (142, 146, 147)
Solar urticaria	Itchy wheals that occur after light (UV and/or visible light) exposure	Rare in general population, 0.08% of patients with CSU (75), 18% of patients who consult a hospital because of sunlight-related skin problems (147)	3–6 years (148–150)
Vibratory angioedema	Cutaneous swellings immediately after exposure to vibration	Very rare, no data available	Very rare, no data available
Cholinergic Urticaria	Itchy wheals after active or passive warming	4–11.2% of population (151–153)	4–7.5 years (154, 155)
Aquagenic urticaria	Itchy wheals or angioedema after skin contact with water	Very rare, no data available	Very rare, no data available
Contact Urticaria	Itchy wheals or angioedema after contact with eliciting agent	Variable, depending on elicitor	Variable, depending on elicitor

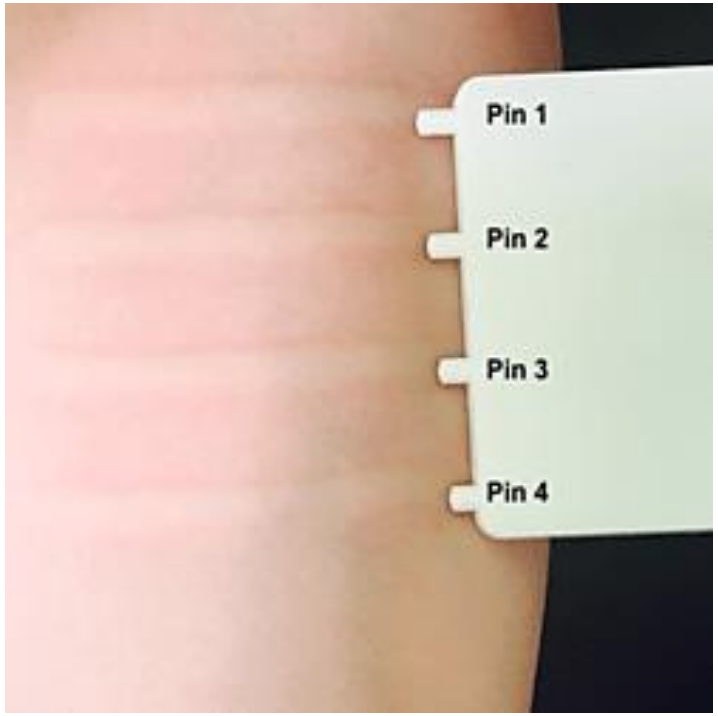
*For most CIndUs, no reliable data on prevalence, incidence, and duration are available. The data presented are largely based on observational studies in small, preselected populations rather than from well-designed epidemiological studies.

Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, B., Bernstein, J. A., Bin
EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy: European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.13397
A. Wesley Burks. (2019). Middleton's Allergy Principles and Practice.

Symptomatic dermatographism

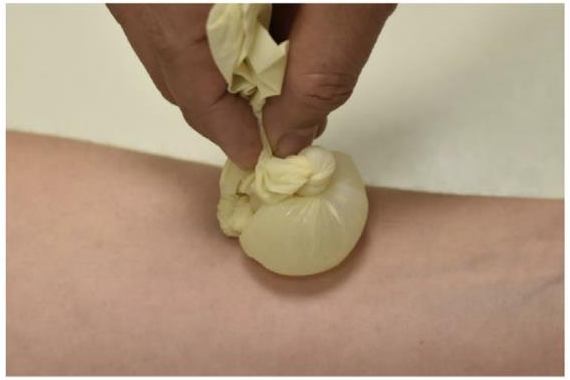
- Triggered by friction/pressure/force on the skin
- Typical distribution includes area of tight clothing
- Common cause of pruritus NYD
- Affects up to 5% of population



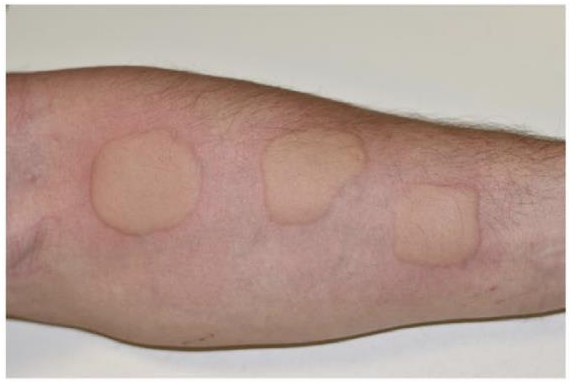


Cold induced urticaria

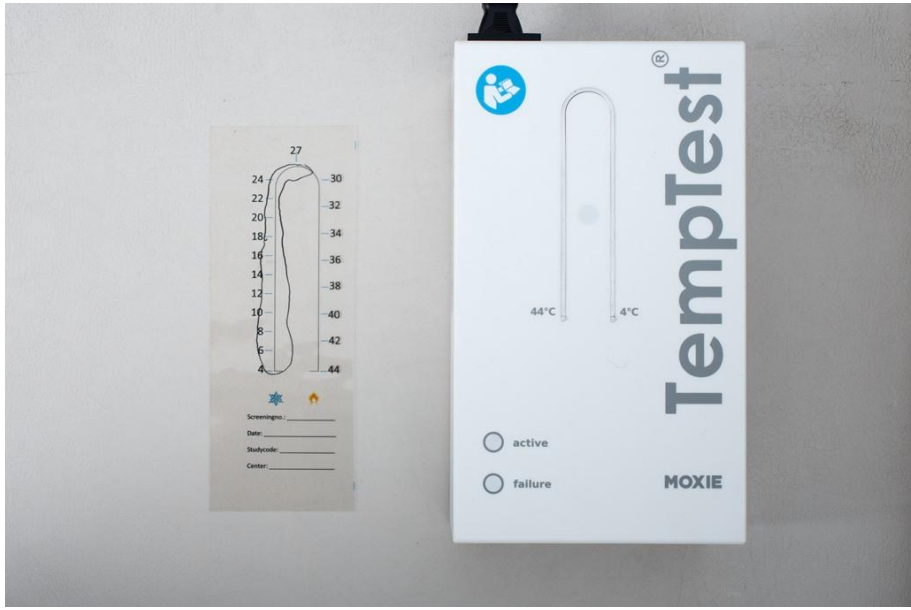
- Triggered by cold contact
- ***Exception – up to 1/3 of patients can have systemic reactions
  - Risk of death from anaphylaxis upon cold water exposure
  - Small number of patients can have throat symptoms with cold drinks
  - I typically prescribe an epinephrine autoinjector in cold induced urticaria



(A) Cold stimulation test (CST) using an ice cube



(B) Ice cube test results



Cold induced urticaria

TABLE 7 Recommendations to the patients with ColdU

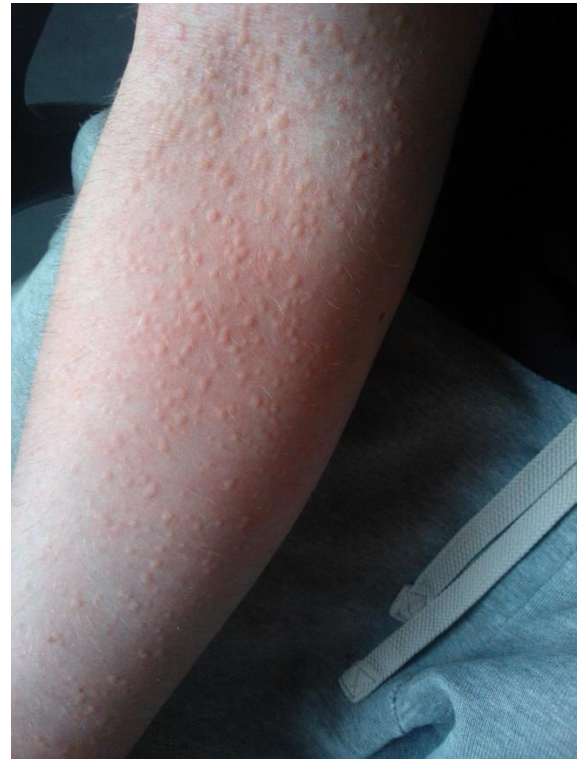
Lifestyle modifications for the patients with ColdU	
Be careful visiting places with low ambient temperature:	Supermarkets (departments with refrigeration)
	Warehouses, cellars
	Rooms with active use of air conditioners, especially in the warm season (shops, public transport, offices)
	Skating rinks, ice arenas
	Cosmetology, dental and treatment rooms
Take precautions when travelling to:	Caves
	Mountains
	Mountain rivers and lakes
Be cautious while doing household activities:	Defrosting the refrigerator
	Window cleaning
Avoid cosmetic procedures involving an exposure to cold:	Cryorejuvenating therapy (cryocapsule, etc)
Avoid:	Ice cream
	Ice
	Fruits and vegetables without pre-warming when stored in the refrigerator
	Cold foods, drinks (temperature should not be below 24°C)
Refrain from water and winter sports:	Swimming
	Diving
	Water polo
	Hockey
	Figure skating
	Skiing, snowboarding
	Curling
High-risk occupations include:	Scuba divers
	Butchers, workers of warehouses and departments of frozen products
	Sailors, fishermen, cooks
	Polar explorers
	Climbers
	Pathologists, surgeons, anaesthesiologists
Recommendations for the perioperative management of ColdU patients	
Air temperature control in the operating room	
Monitoring the patient's body temperature, blood pressure, heart rate, breathing rate. Should systemic reactions occur, use epinephrine and glucocorticoids.	
Use of premedication (glucocorticoids, antihistamines)	
Pre-warming of solutions for parenteral use	
Warming the patient during surgery (blankets, heaters)	
Avoid using chloroethyl, treating large skin surfaces with alcohol and antiseptic solutions, do not use ice and cooling elements.	

Cold induced urticaria - mimickers

- Differential diagnoses in patients with potential cold urticaria
  - Typically have an atypical feature – e.g. negative ice cube test, or persistent rash
- Cryopyrin-associated periodic syndrome (CAPS)
  - Secondary to genetic abnormality in *NLRP3* gene
  - Familial cold autoinflammatory syndrome (FCAS)
  - Muckle-Wells Syndrome
  - Neonatal-onset multisystem inflammatory disease (NOMID)
- PLC-gamma-2-associated antibody deficiency and immune dysregulation (PLAID)
- Cryoglobulinemic vasculitis

Cholinergic urticaria

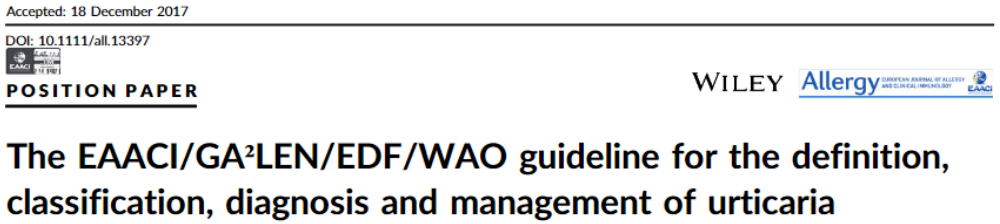
- Named initially because of induction with methacholine
- Triggered by increases in body heat, e.g. exercise, spicy foods, hot shower
- Lesions typically more pinpoint



Approach to Urticaria

Most pertinent details on history:

1. Is this hives?
   - Onset of disease
   - Characteristic of rash, including pattern of distribution
2. Acute or chronic?
   - Duration of symptoms (? >6 weeks)
3. Is there associated angioedema?
4. Identified triggers?
   - Acute: food, medications, venom, latex, infection
   - Chronic: infections, stress, NSAIDs, alcohol, physical triggers
5. Red flag features of systemic disorders?
   - Painful, scarring, prolonged rash?
   - Associated symptoms – fever, joint pain, family history, constitutional symptoms
6. **Prior treatments?**



Adapted from Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, B., Bernstein, J. A., Bindslev-Jensen, C., Brzoza, Z., Buense Bedrikow, R., Canonica, G. W., Church, M. K., Craig, T., Danilycheva, I. V., Dressler, C., Ensina, L. F., Giménez-Arnau, A., Godse, K., Gonçalo, M., ... Maurer, M. (2018). The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy: European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.13397

Chronic urticaria - Treatment

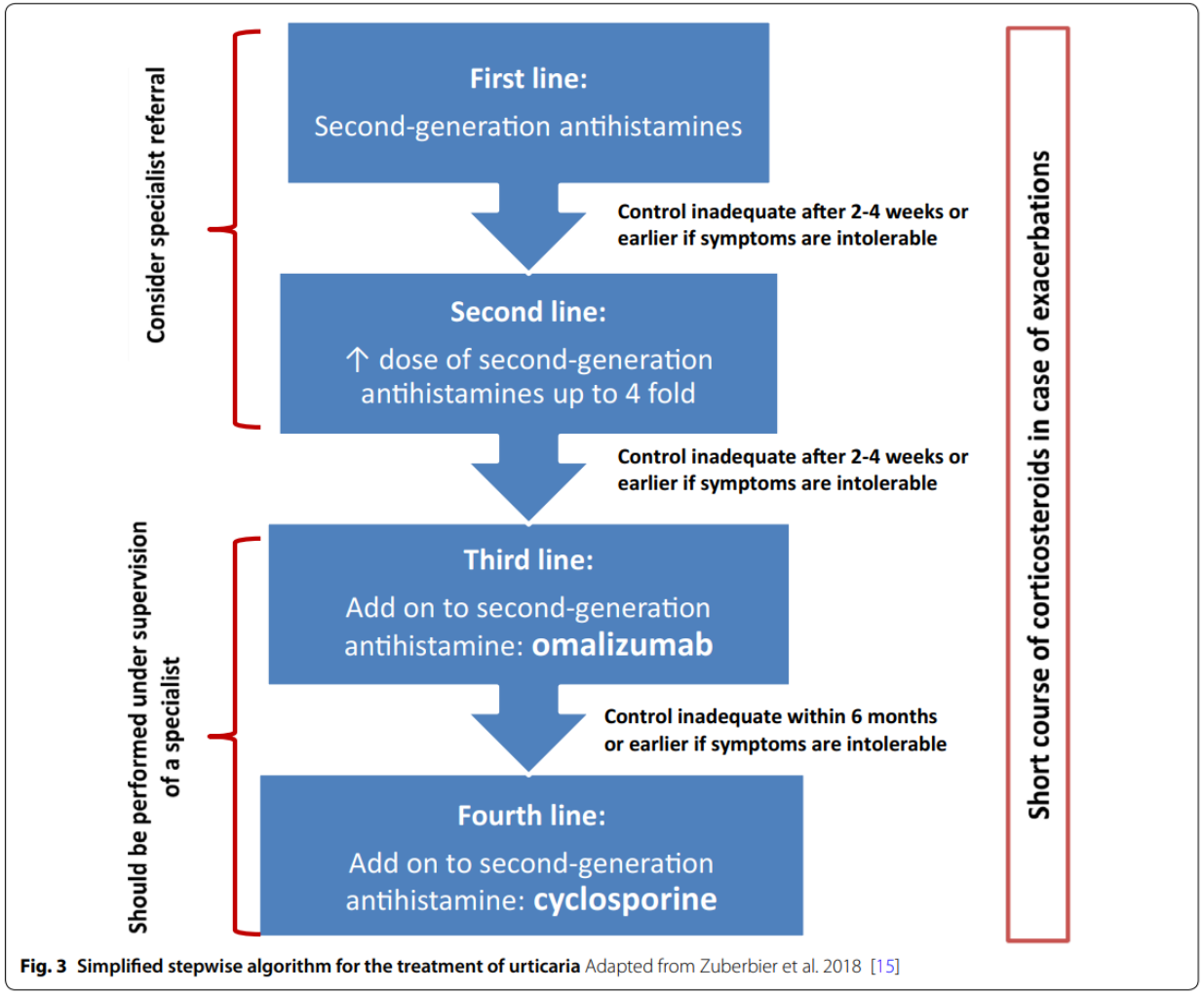


Fig. 3 Simplified stepwise algorithm for the treatment of urticaria Adapted from Zuberbier et al. 2018 [15]

Kanani, A., Betschel, S. D., & Warrington, R. (2018). Urticaria and angioedema. Allergy, Asthma & Clinical Immunology, 14(S2), 59. https://doi.org/10.1186/s13223-018-0288-z

Chronic urticaria - Treatment

4x dose??

Atopic dermatitis and skin disease

The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria

Maria Staevska, MD,[a] Todor A. Popov, MD, PhD,[a] Tanya Kralimarkova, MD,[a] Cvetelina Lazarova, MD,[a] Steliana Kraeva, MD,[a] Dora Popova, MD, PhD,[a] Diana S. Church, MD,[b] Vasil Dimitrov, MD, PhD,[a] and Martin K. Church, PhD, DSc[b,c] *Sofia, Bulgaria, Southampton, United Kingdom, and Berlin, Germany*

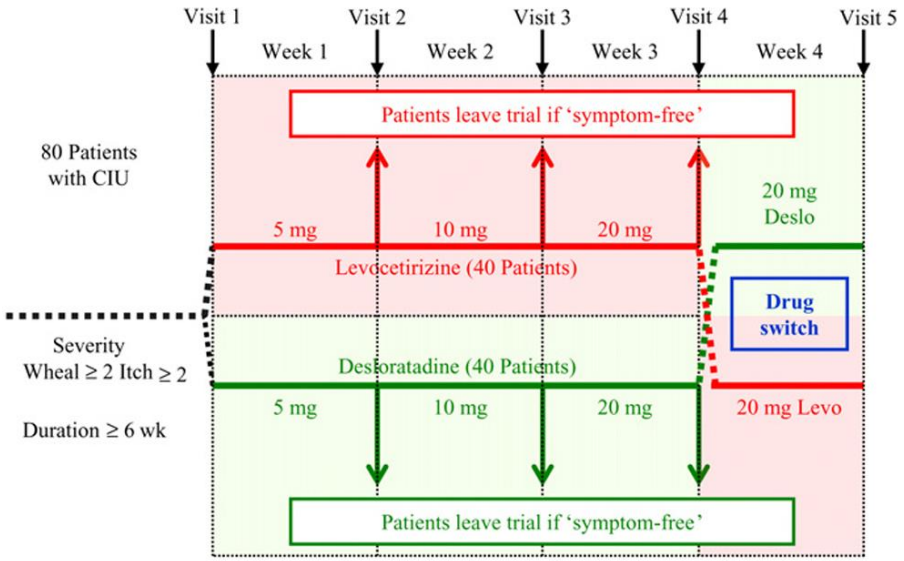


FIG 1. The study design with the treatment arms and the crossover step. *Deslo,* Desloratadine; *Levo,* levocetirizine.

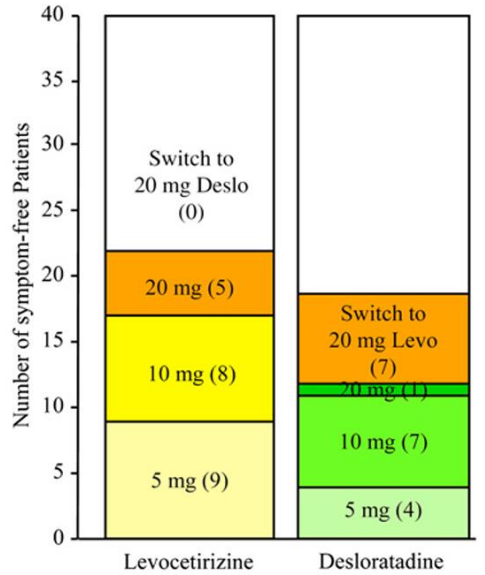
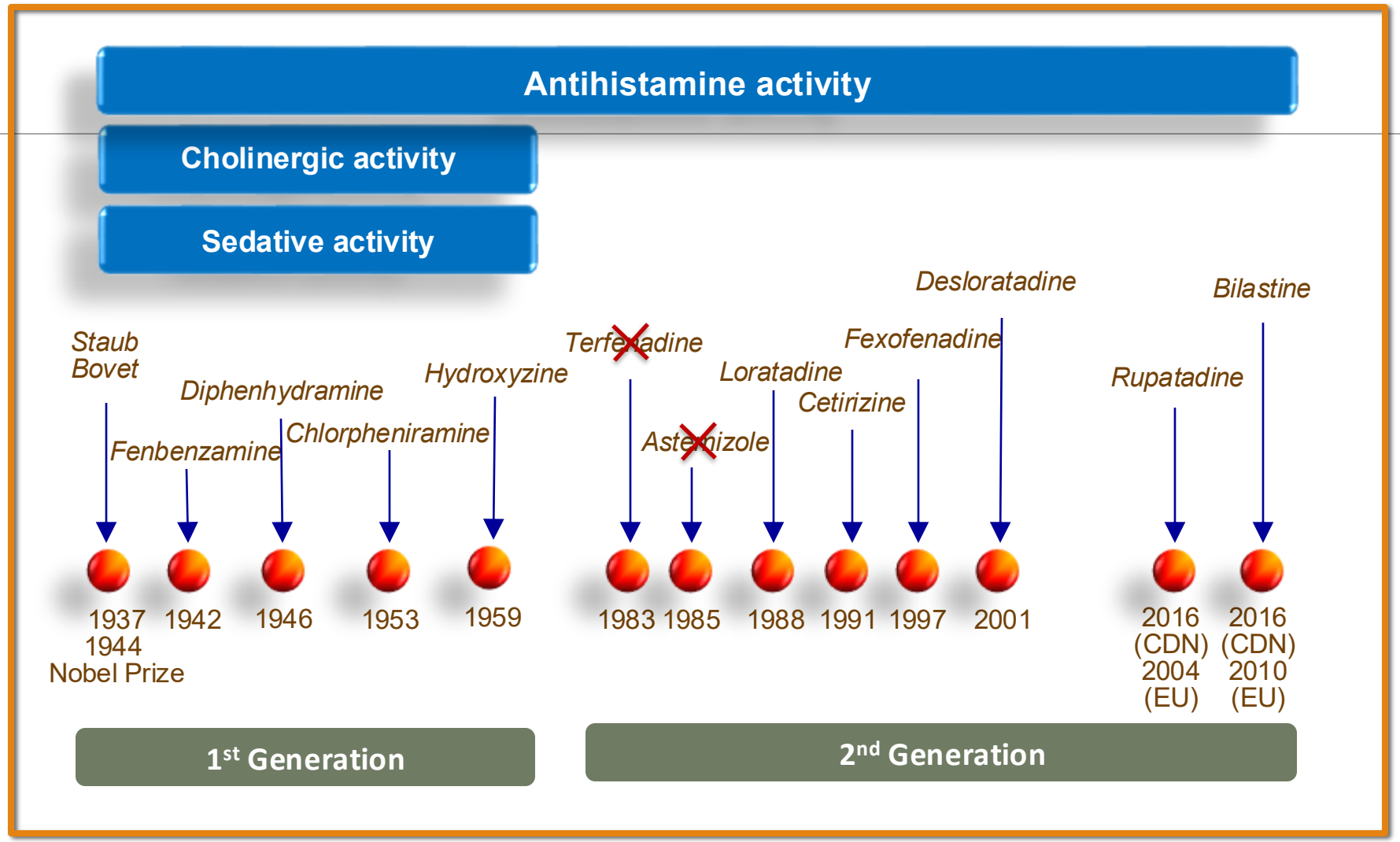


FIG 2. The number of patients whose symptoms were relieved by levocetirizine *(Levo)* or desloratadine *(Deslo)* throughout the 4 weeks of the study. The *numbers in parentheses* refer to the number of patients who were symptom free on 5 mg (week 1), 10 mg (week 2), 20 mg (week 3), or after the drug switch (week 4).



Terfenadine and astemizole were removed from the Canadian market in 1997

Adapted from Kuna et al., Adv Dermatol Allergol 2016; 33(6): 397-410.

First generation antihistamines

More side effects

- Sedation
- Cognitive impairment
- Association with dementia in long tern

Fein *et al.*
Allergy Asthma Clin Immunol (2019) 15:61
https://doi.org/10.1186/s13223-019-0375-9

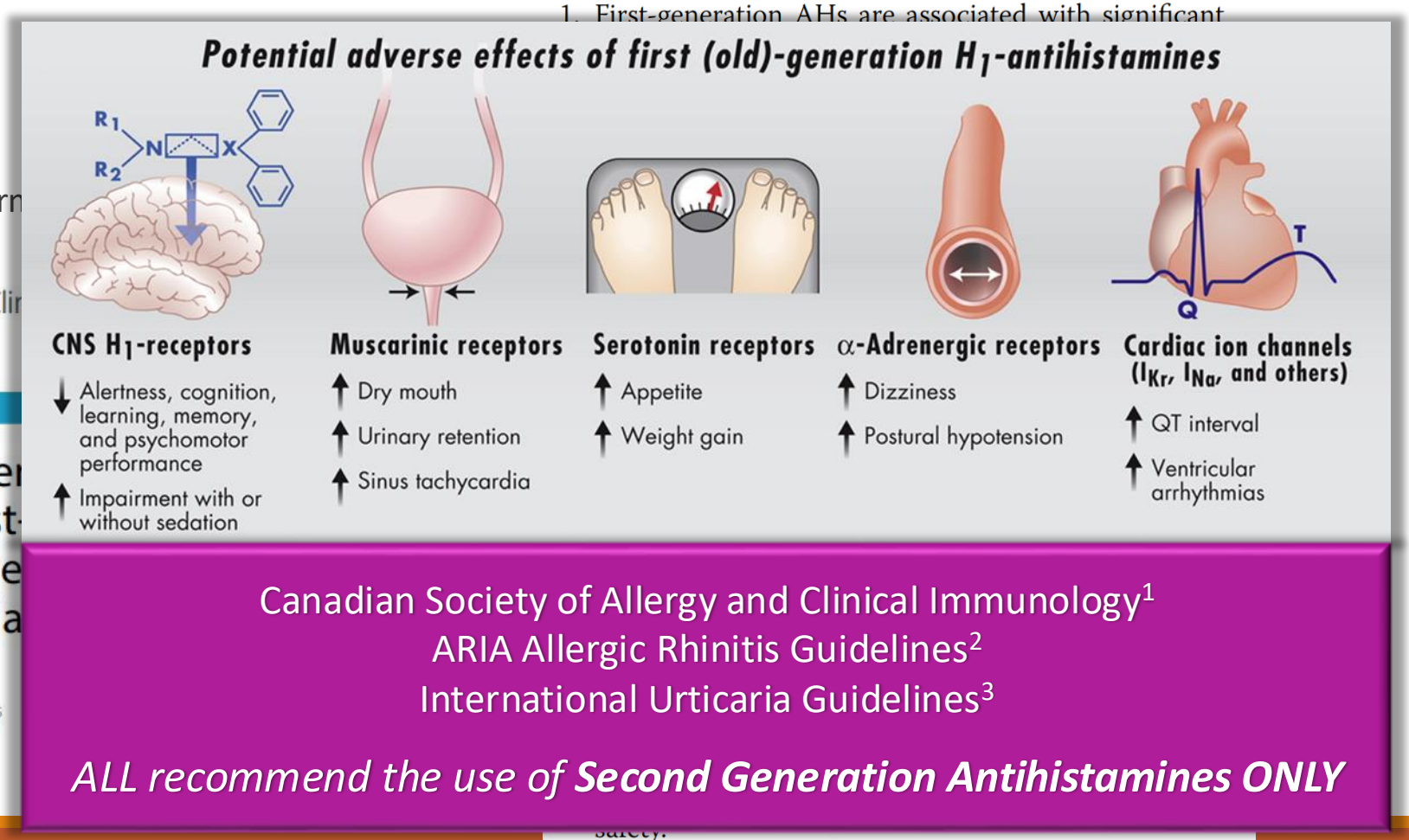
Allergy, Asthma & Clin

REVIEW

CSACI position statement: Newer ge
H_1-antihistamines are safer than first-
H_1-antihistamines and should be the
antihistamines for the treatment of a
rhinitis and urticaria

Michael N. Fein[1], David A. Fischer[2,3*], Andrew W. O'Keefe[4] and Gord L. Sussman[5]

1. First-generation AHs are associated with significant



Canadian Society of Allergy and Clinical Immunology[1]
ARIA Allergic Rhinitis Guidelines[2]
International Urticaria Guidelines[3]

ALL recommend the use of ***Second Generation Antihistamines ONLY***

safety.

Image: Simons & Simons. J Allergy Clin Immunol 2011;128:1139-50

2nd Generation Antihistamines Available in Canada

Table 2 Antihistamines commonly used and indicated for the treatment o

Second-generation H1-receptor antihistamines	Standard adult dose (mg daily)	4 times standard adult dose (mg daily)
Cetirizine (Reactine)	10–20	40
Desloratadine (Aerius)	5	20
Fexofenadine (Allegra)	120	480
Loratadine (Claritin)	10	40
Bilastine (Blexten)	20	80
Rupatadine (Rupall)	10	40

The NEW ENGLAND JOURNAL of MEDICINE

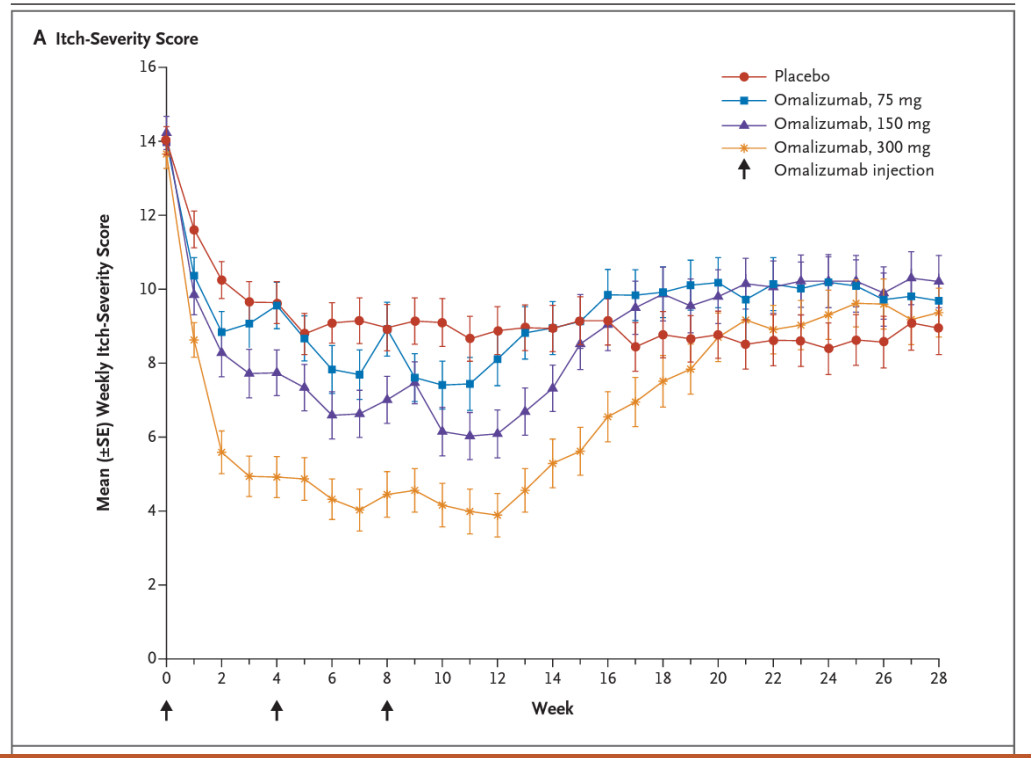
ORIGINAL ARTICLE

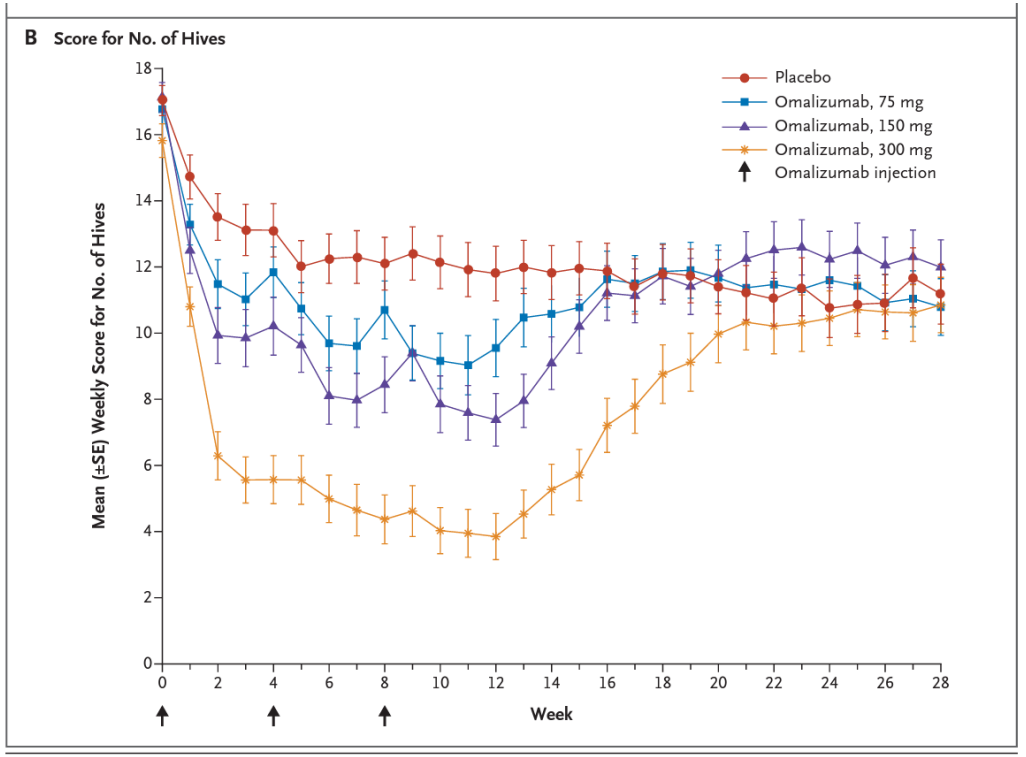
Chronic urticaria - Omalizumab

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

Marcus Maurer, M.D., Karin Rosén, M.D., Ph.D., Hsin-Ju Hsieh, Ph.D., Sarbjit Saini, M.D., Clive Grattan, M.D., Ana Gimenéz-Arnau, M.D., Ph.D., Sunil Agarwal, M.D., Ramona Doyle, M.D., Janice Canvin, M.D., Allen Kaplan, M.D., and Thomas Casale, M.D.

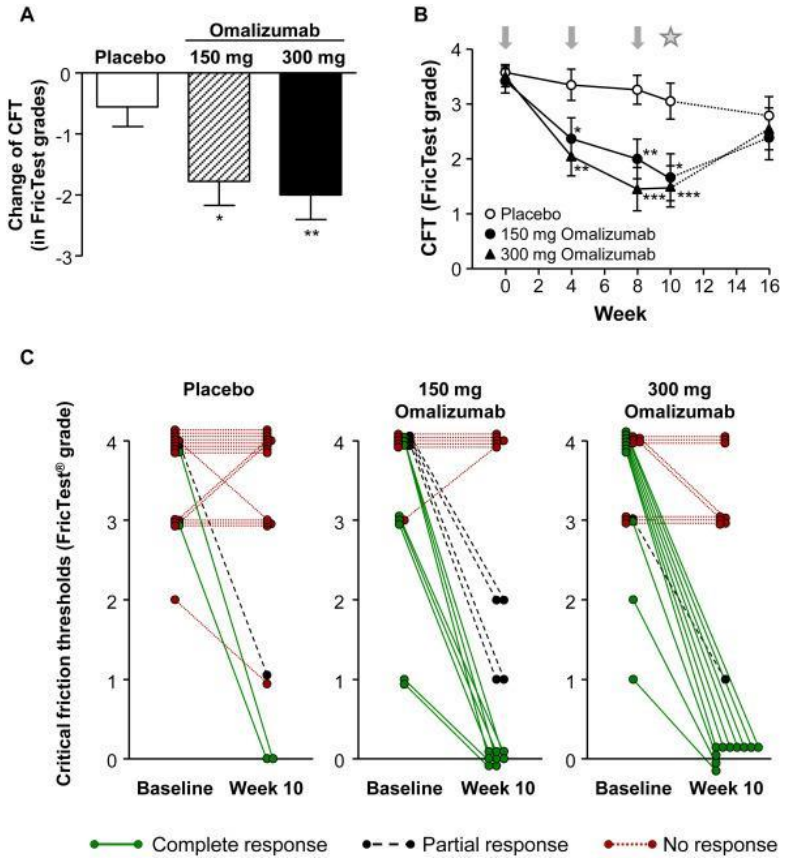
- Anti-IgE antibody
- Typical dose for CSU: Omalizumab 300mg subcut q4weeks
- Begin at infusion center, then can progress to self administration





Kanani, A., Betschel, S. D., & Warrington, R. (2018). Urticaria and angioedema. Allergy, Asthma & Clinical Immunology, 14(S2), 59. https://doi.org/10.1186/s13223-018-0288-2

Chronic urticaria - Omalizumab



Kanani, A., Betschel, S. D., & Warrington, R. (2018). Urticaria and angioedema. Allergy, Asthma & Clinical Immunology, 14(S2), 59. https://doi.org/10.1186/s13223-018-0288-z

Chronic urticaria - Montelukast

- Montelukast – Leukotriene receptor antagonist
- Typical dose – 10mg po daily
- No strong evidence for effect in urticaria
- Most typically prescribed to satisfy insurance requirements for omalizumab coverage

de Silva *et al. Allergy, Asthma & Clinical Immunology* 2014, **10**:24
http://www.aacijournal.com/content/10/1/24

ALLERGY, ASTHMA & CLINICAL IMMUNOLOGY

REVIEW Open Access

Leukotriene receptor antagonists for chronic urticaria: a systematic review

Nipun Lakshitha de Silva[1], Hasitha Damayanthi[2], Anoja Chamarie Rajapakse[3], Chaturaka Rodrigo[1] and Senaka Rajapakse[1*]

Kanani, A., Betschel, S. D., & Warrington, R. (2018). Urticaria and angioedema. Allergy, Asthma & Clinical Immunology, 14(S2), 59. https://doi.org/10.1186/s13223-018-0288-z

Chronic urticaria – Other treatments?

TABLE 11 Alternative treatment options

Although evidence from publications is low, clinical experience indicates that they may be useful in certain contexts. Interventions are listed in alphabetical order by frequency of use rather than efficacy.		
Intervention	**Substance (class)**	**Indication**
Widely used		
Antidepressant	Doxepin[a]	CSU
Diet	Pseudoallergen-free diet[b]	CSU
H_2-antihistamine	Ranitidine[c]	CSU
Immunosuppressive	Methotrexate^Mycophenolate mofetil	CSU +/− DPU[d] Autoimmune CSU
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulphones	Dapsone, Sulphasalazine	CSU +/− DPU CSU +/− DPU
Infrequently used		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	IVIG^Plasmapheresis	Autoimmune CSU Autoimmune CSU
Miscellaneous	Autologous blood/serum Hydroxychloroquine	CSU CSU
Phototherapy	Narrow-band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
Rarely used		
Anticoagulant	Heparin	CSU
Immunosuppressive	Cyclophosphamide Rituximab	Autoimmune CSU Autoimmune CSU
Miscellaneous	Anakinra	DPU
	Anti-TNF-alpha	CSU +/− DPU
	Camostat mesilate	CSU
	Colchicine	CSU
	Miltefosine	CSU
	Mirtazepine	CSU
	PUVA	CSU
Very rarely used		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D	CSU
	Interferon alpha	CSU

[a]Has also H_1- and H_3-antihistaminergic properties.

Kanani, A., Betschel, S. D., & Warrington, R. (2018). Urticaria and angioedema. Allergy, Asthma & Clinical Immunology, 14(S2), 59. https://doi.org/10.1186/s13223-018-0288-z

Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials

METHODS

CUPID Study A

138 patients

Aged ≥ 6 years

Omalizumab-naïve

The primary and key secondary endpoints were changes from BL to week 24 in UAS7[a] and ISS7[b] respectively, or vice versa depending on regional regulatory requirements.

CUPID Study B

108 patients

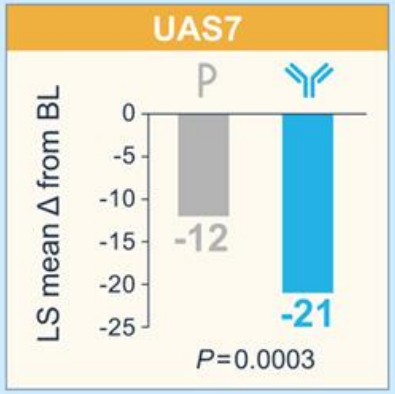
Aged ≥ 12 years

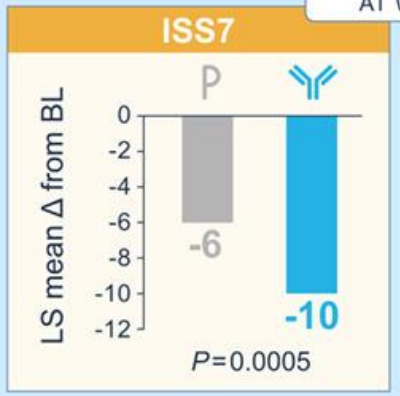
Omalizumab-intolerant/ incomplete responders

SAFETY OUTCOMES:

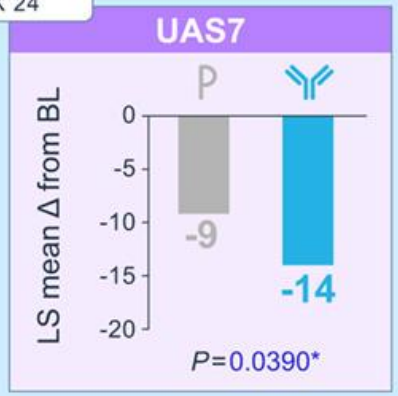
- Pooled safety data were consistent between dupilumab and placebo and with the known dupilumab safety profile.

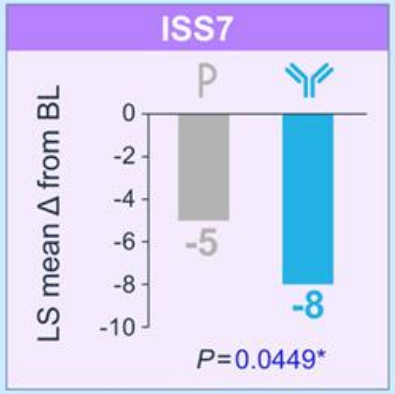
RESULTS
AT WEEK 24





In Study A, both UAS7 and ISS7 improved significantly with dupilumab vs placebo at week 24.





In Study B, UAS7 improved significantly (primary endpoint for EU countries), with a numerical, non-significant trend of improvement in ISS7 (primary endpoint for non-EU countries).

*Significance was tested at alpha 0.043 after the protocol pre-specified efficacy statistical criteria for futility was met. UAS7 was statistically significant (primary endpoint for EU countries); ISS7 did not meet significance (primary endpoint for non-EU countries).

P	Placebo
Y	Dupilumab
BL	Baseline
EU	European Union
LS	Least squares
Δ	Change

[a] UAS7: Urticaria Activity Score over 7 days (range: 0-42).

[b] ISS7: Itch Severity Score over 7 days (range: 0-21).

The NEW ENGLAND JOURNAL of MEDICINE

Remibrutinib in Chronic Spontaneous Urticaria

A Research Summary based on Metz M et al. | 10.1056/NEJMoa2408792 | Published on March 6, 2025

WHY WERE THE TRIALS DONE?

Second-generation H_1-antihistamines are first-line treatments for chronic spontaneous urticaria; however, more than 50% of patients still have symptoms during treatment. In early studies, remibrutinib, a Bruton's tyrosine kinase inhibitor, appeared to be safe and efficacious in patients who continued to have symptoms with second-generation H_1-antihistamines. Additional data are needed.

HOW WERE THE TRIALS CONDUCTED?

In two identical trials (REMIX-1 and REMIX-2), adults with chronic spontaneous urticaria that remained symptomatic during treatment with second-generation H_1-antihistamines were randomly assigned to receive oral remibrutinib or placebo in addition to background therapy with an H_1-antihistamine. The primary end point was the change at week 12 in the urticaria activity score during a 7-day period (UAS7; scores range from 0 to 42, with higher scores indicating greater severity of itching and hives).

TRIAL DESIGN

- Phase 3
- Multicenter
- Double-blind
- Randomized
- Placebo-controlled

RESULTS

In both trials, improvement in the UAS7 at week 12 was significantly greater with remibrutinib than with placebo. The percentage of patients with a UAS7 of 6 or lower at week 12 (a secondary end point) was also significantly higher with remibrutinib than with placebo. Remibrutinib had a fast onset of action, with improvements reported as early as week 1. Adverse events and serious adverse events occurred with similar frequency in the groups, although petechiae occurred more often with remibrutinib.

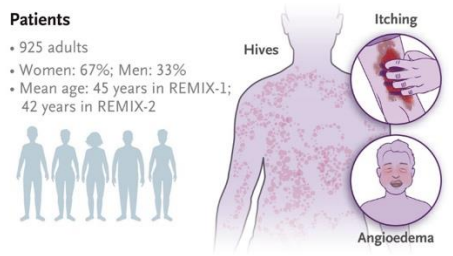
LIMITATIONS AND REMAINING QUESTIONS

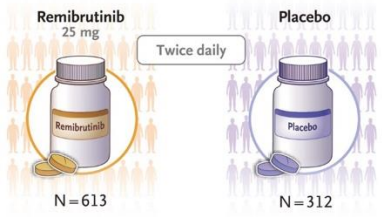
- Twelve patients who underwent randomization by mistake and one patient deemed to be nonadherent were not included in the full analysis population.
- Patients who received placebo had decreases in symptoms throughout the trials, which may have been due to background medication and additional rescue medication.

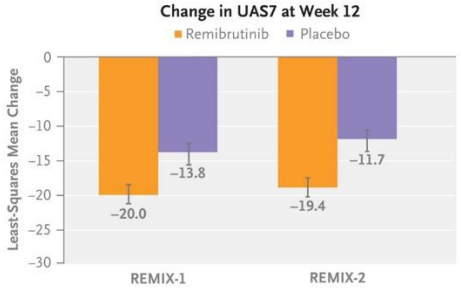
CONCLUSIONS

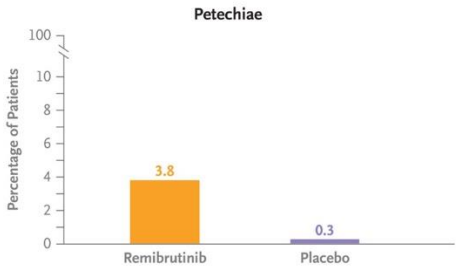
In adults with chronic spontaneous urticaria that remained symptomatic during treatment with second-generation H_1-antihistamines, remibrutinib led to greater decreases in symptoms at week 12 than placebo.

NEJM QUICK TAKE









Copyright © 2025 Massachusetts Medical Society.

Case 1

Angela is a 28 year-old woman who presents with a 6 month history of **intermittent rash** on the body. She has also been having episodes of **lip and eye swelling**. It started after she got the COVID-19 vaccine. The rash is very bothersome, and she is unable to sleep well. There has partial improvement with use of cetirizine PRN.

She describes the rash as transient, erythematous and pruritic, suggestive of urticaria.
There are no red flag features.

You send for CBC, CRP, Total IgE, Anti-TPO and they were all unremarkable.

You recommend cetirizine up to 40mg daily, and there is complete relief.

Angioedema?

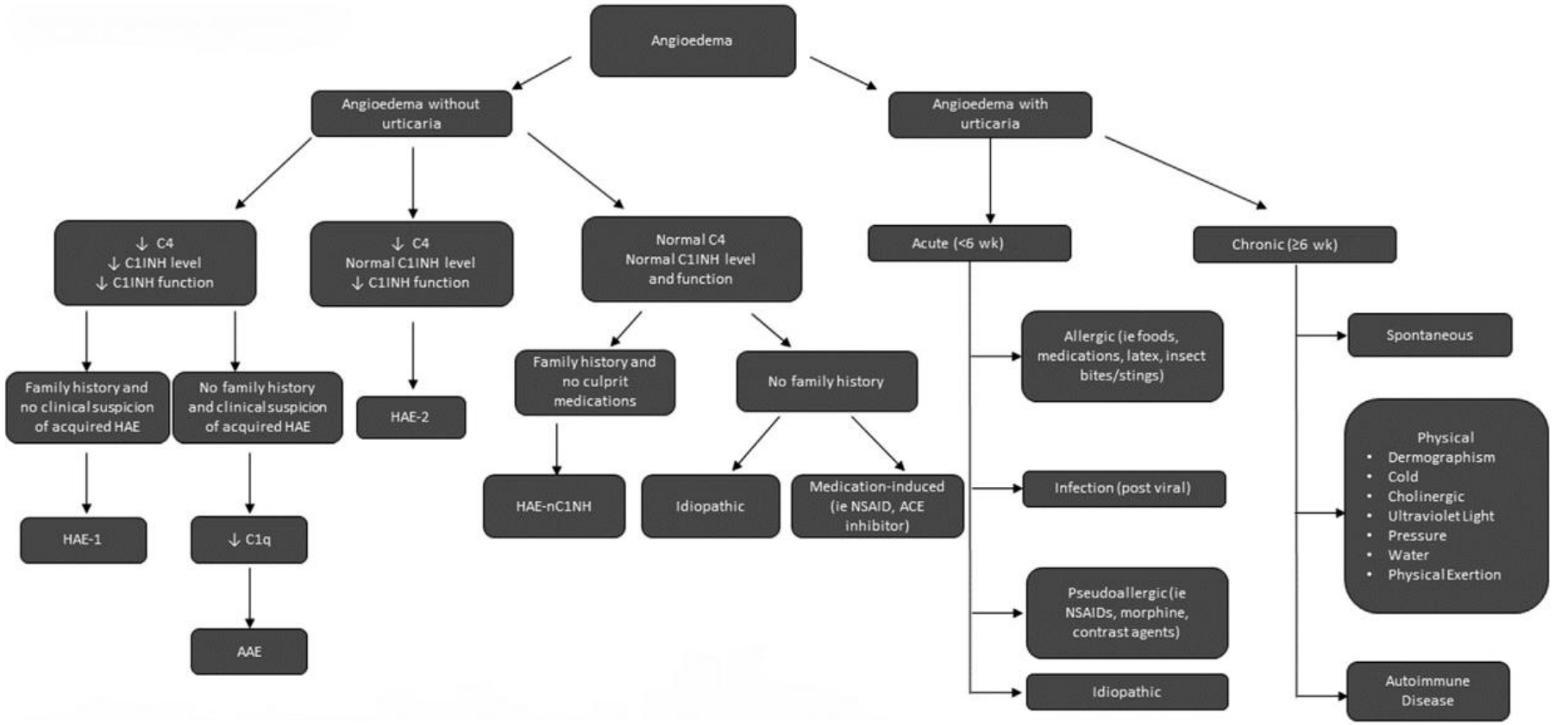


Fig. 5. Angioedema algorithm. AAE, acquired angioedema; C1INH, C1 esterase inhibitor; HAE-nC1NH, hereditary angioedema with normal C1 esterase inhibitor.

Gill, P., & Betschel, S. D. (2017). The Clinical Evaluation of Angioedema. Immunology and Allergy Clinics of North America. https://doi.org/10.1016/j.iac.2017.04.007

Kinin-mediated Pathway

Common causes:

- Drug induced angioedema
- Hereditary angioedema
- Acquired angioedema

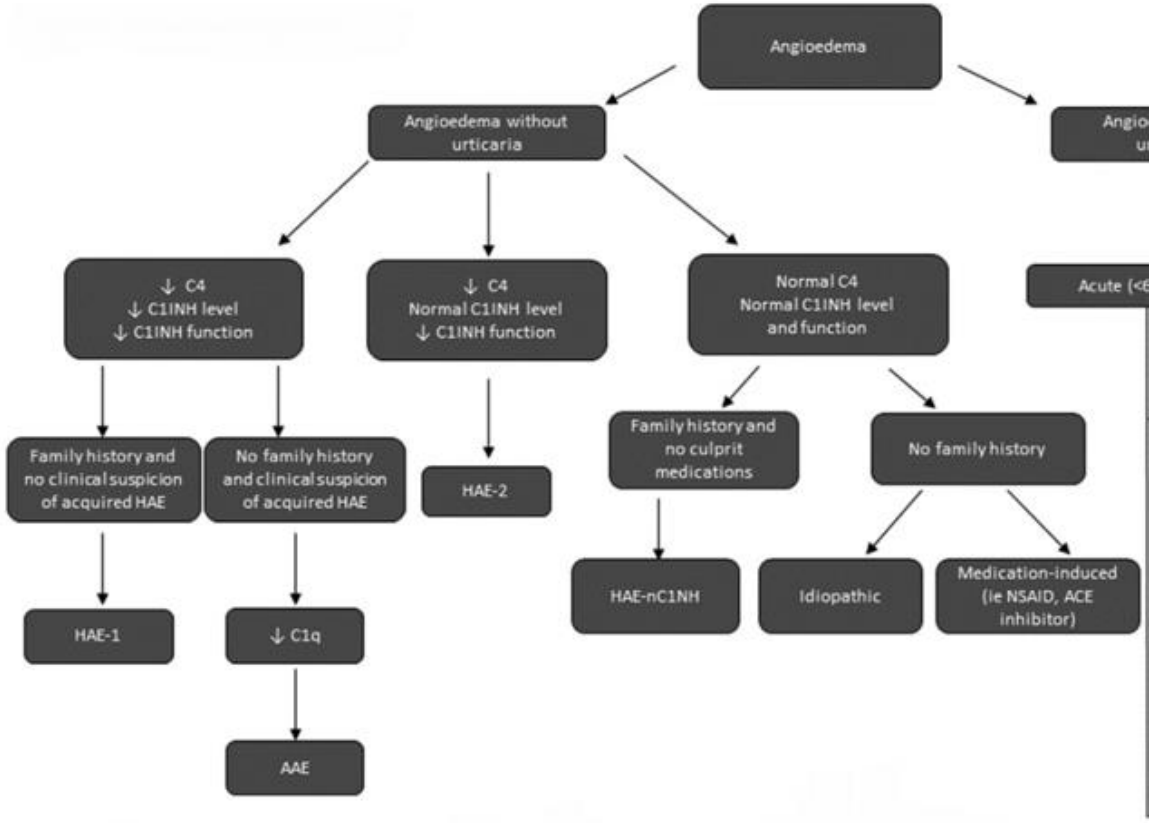


Fig. 5. Angioedema algorithm. AAE, acquired angioedema; C1INH, C1 esterase inhibitor; HAE

Gill, P., & Betschel, S. D. (2017). The Clinical Evaluation of Angioedema. Immunology and Allergy Clinics of North America. https://doi.org/10.1016/j.iac.2017.04.007

Clinical Differences

Histamine vs bradykinin

- Histamine-mediated
  - Tend to be associated with urticaria
    - 10% of patients only have angioedema
  - Responsive to
    - Antihistamines
    - Steroids
    - Epinephrine
  - Duration is shorter

S1 Table: Mast cell (histamine) versus bradykinin mediated angioedema

Characteristic	Mast cell (histamine)	Bradykinin
Rate of onset	Minutes	Hours
Duration of swelling	24 – <48 hours	>48 hours
Urticaria	+	–
Pruritis	+	–
Pain/burning	–	May be present
Response to antihistamine	+	–
Response to corticosteroids	+	–

+ = Present, – = Not commonly present

Busse, P. J., & Christiansen, S. C. (2020). Hereditary Angioedema. The New England Journal of Medicine, 382, 1136–1148.

Case 2

Charles is a 65 year-old man with intermittent lip swelling for the past few months. No clear triggers have been identified. The swelling gradually worsens over hours, and can last up to 3 days. He has tried antihistamines and have not had much relief.

This morning, he also developed an episode of tongue swelling and throat tightness.

What additional info would you like?

Case 2

Swelling:
- Lip, tongue and throat
- Develops slowly over hours
- No overlying skin flaking or cracking
- Symptoms resolve over days

Associated symptoms:
- No abdominal pain, vomiting, dyspnea
- No rash

Treatment:
- Antihistamines ineffective

Potential triggers?
- No new foods, contacts, medications within 1 year

Medical History:
- Hypertension
- Type 2 Diabetes Mellitus

Medications:
- Ramipril
- Janumet (metformin/sitagliptin)
- Atorvastatin

What is the potential diagnosis?

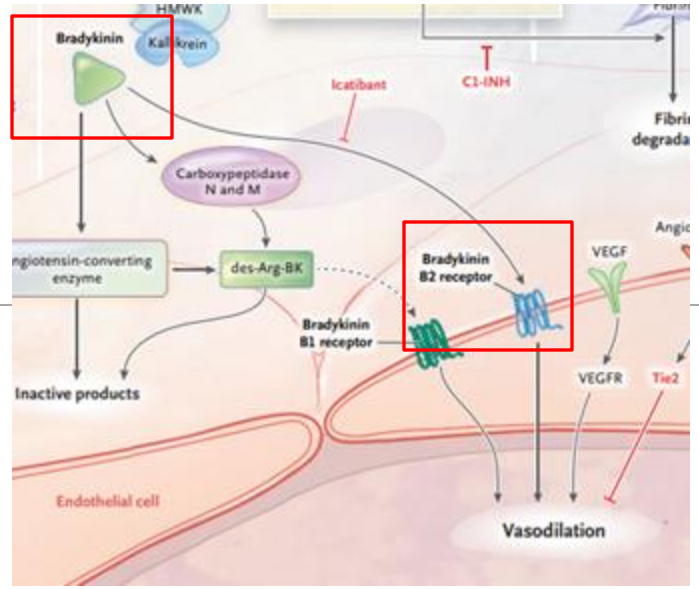
What are treatment options?

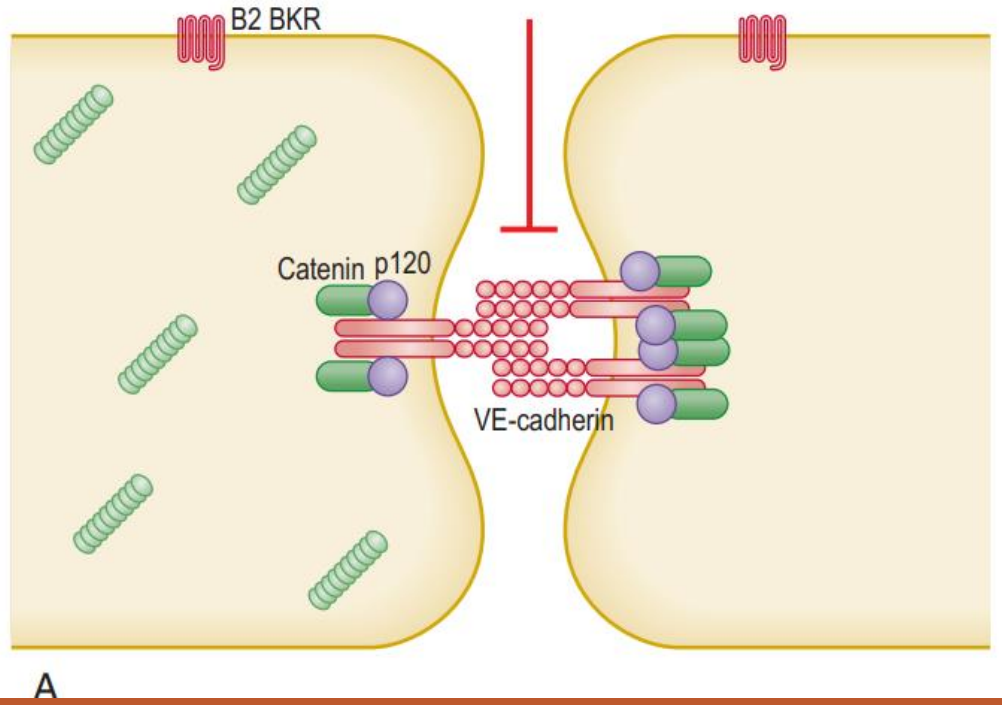
Immune Mechanisms

Kinin-mediated pathway

Bradykinin

- B_2 receptors
- Internalization of cadherin
- Loss of endothelial tight junction
- Increased cell permeability

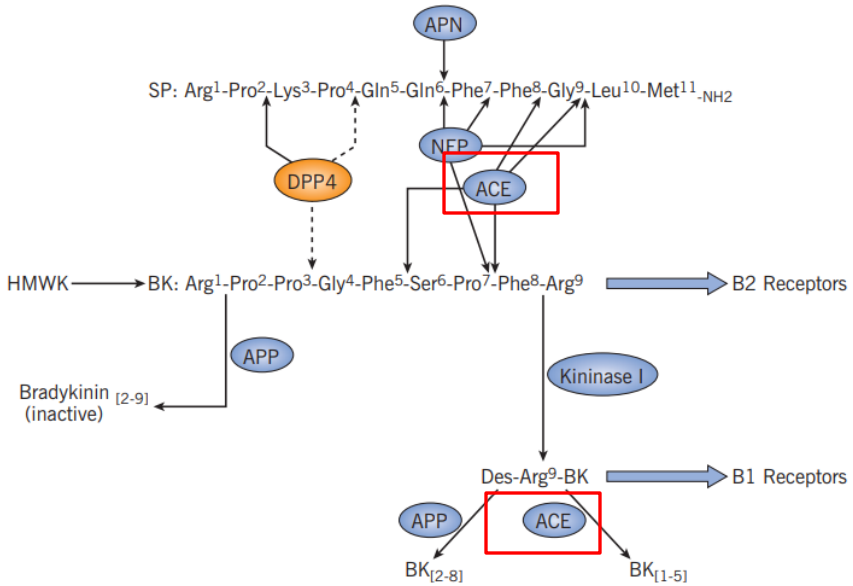




Busse, P. J., & Christiansen, S. C. (2020). Hereditary Angioedema. The New England Journal of Medicine, 382, 1136–1148.
N. Franklin Adkinson Jr. (2014). Middleton'S Allergy Principles and Practice. Middleton's Allergy 2-Volume Set.

Drug-induced Angioedema

Degradation of bradykinin



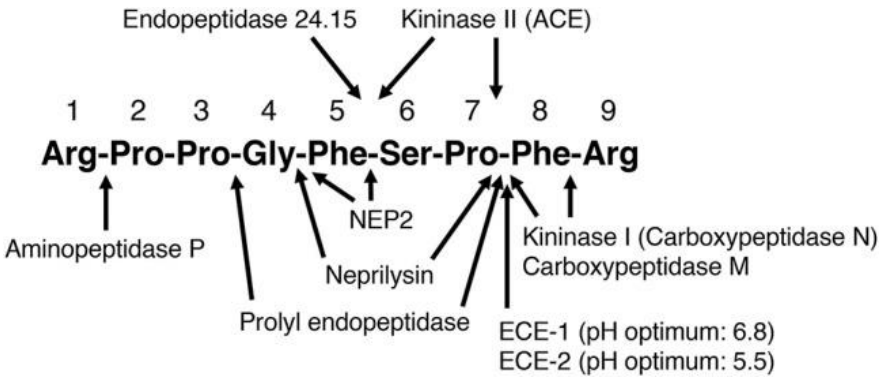


Fig. 12.6 Degradation of bradykinin, des-Arg9-bradykinin, and substance P. APN, aminopeptidase N or M; APP, aminopeptidase P; BK, bradykinin; DPP4, depeptidyl peptidase IV; HMWK, high-molecular-weight kininogen; NEP, neutral endopeptidase; SP, substance P. (From Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin N Am 2006; 26:725–737.)

Marcus Maurer, Clive EH Grattan, Bruce L Zuraw, 12 - Urticaria and angioedema without wheals, Editor(s): Stephen T Holgate, Martin K Church, David H Broide, Fernando D Martinez, Allergy (Fourth Edition), W.B. Saunders, 2012, Pages 247-261, ISBN 9780723436584, https://doi.org/10.1016/B978-0-7234-3658-4.00016-0.

Multicenter study of patients with angiotensin-converting enzyme inhibitor–induced angioedema who present to the emergency department

Aleena Banerji, MD*; Sunday Clark, MPH, ScD†; Michelle Blanda, MD‡; Frank LoVecchio, DO§; Brian Snyder, MD‖; and Carlos A. Camargo Jr, MD, DrPH¶

ACE-inhibitor Induced Angioedema

- 0.7 per 10,000 ED visits
- 58% sent home from ED
- 18% admitted for observation
- 12% ward admission
- 11% ICU admission

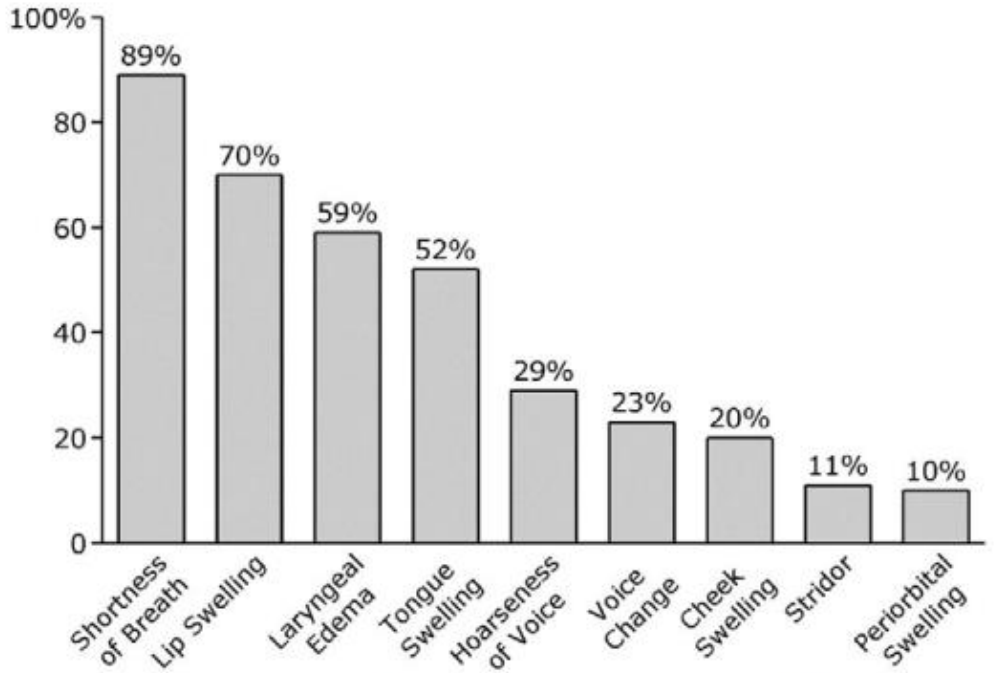


Figure 2. Symptoms of angiotensin-converting enzyme inhibitor–induced angioedema at initial presentation to the emergency department.

ACE-inhibitor Induced Angioedema

Epidemiology

- Prevalence
  - 0.3% of patients on ACEi
  - Increased risk (3 times) in black patients
  - Up to 40% of US ED visits for angioedema
- Sex
  - F > M
- Age
  - Increased risk >65
- Not drug- or dose- specific

Hypertension
Volume 51, Issue 6, 1 June 2008; Pages 1624-1630
https://doi.org/10.1161/HYPERTENSIONAHA.108.110270

RENIN-ANGIOTENSIN SYSTEM

Angioedema Incidence in US Veterans Initiating Angiotensin-Converting Enzyme Inhibitors

Donald R. Miller, Susan A. Oliveria, Dan R. Berlowitz, Benjamin G. Fincke, Paul Stang, and David E. Lillienfeld

Table 3. Relative Risk Estimates* for Angioedema in VA Patients Prescribed ACE or Other Antihypertensives (Table view)

Variable	Reference Category	Relative Risk*	95% Confidence Intervals
Initiating ACE	other AH	3.56	2.82 to 4.44
Black	white	3.88	2.99 to 4.95
Other race	white	0.91	0.77 to 1.13
Female	male	1.45	1.15 to 1.88
Age <45 years	75+ years	1.17	0.78 to 1.77
Age 45 to 54 years	75+ years	0.90	0.80 to 1.04
Age 55 to 64 years	75+ years	1.17	0.91 to 1.51
Age 65 to 74 years	75+ years	1.42	1.15 to 1.74
Chronic heart failure	No CHF	1.22	1.08 to 1.38
Coronary artery disease	No CAD	1.31	1.16 to 1.48
Diabetes mellitus	No DM	0.88	0.82 to 0.95
ACE initiated: in separate model			
Lisinopril	other AH	3.63	2.34 to 5.48
Fosinopril	other AH	3.45	2.06 to 5.46
Captopril	other AH	2.20	1.08 to 3.95
*Estimated from multivariate Poisson regression models.			

Makani, H., Messerli, F. H., Romero, J., Wever-Pinzon, O., Korniyenko, A., Berrios, R. S., & Bangalore, S. (2012). Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. American Journal of Cardiology. https://doi.org/10.1016/j.amjcard.2012.03.034
Lewis, L. M. (2013). Angioedema: Etiology, pathophysiology, current and emerging therapies. Journal of Emergency Medicine. https://doi.org/10.1016/j.jemermed.2013.03.045
Cicardi, M., Aberer, W., Banerji, A., Bas, M., Bernstein, J. A., Bork, K., ... Zuraw, B. (2014). Classification, diagnosis, and approach to treatment for angioedema: Consensus report from the Hereditary Angioedema International Working Group. Allergy: European Journal of Allergy and Clinical Immunology, 69(5). https://doi.org/10.1111/all.12380
Beltrami, L., Zanichelli, A., Zingale, L., Vacchini, R., Carugo, S., & Cicardi, M. (2011). Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. Journal of Hypertension. https://doi.org/10.1097/HJH.0b013e32834b4b9b

ACE-inhibitor Induced Angioedema

Symptoms

- Most commonly localized to face (85%), then lips, eyelids, tongue, neck, and upper airways
- Gastrointestinal angioedema reported
- Laryngeal edema (10%) may be fatal

Timing

- 50% of cases occur within first week of initiation
- May occur after years of therapy
- May occur after discontinuation of therapy
  - 46% experienced recurrence,
    88% - first recurrence within 1 month;
    only 2% had recurrence after 3 months

Table 2. Angioedema Rates Among Patients Initiating ACE or Other Antihypertensives (OAH)—April 1999 to December 2000 (Table view)

Time of Angioedema	Initiating ACE (n=195 192)				Initiating OAH (n=399 889)			
	Person-Years n	Cases n	Per 1000 Person-Years		Person-Years n	Cases n	Per 1000 Person-Years	
			Rate	95% CI			Rate	95% CI
All	315 527	434	1.38	1.25 to 1.51	738 250	399	0.54	0.49 to 0.60
Before drug use	89 547	42	0.47	0.34 to 0.63	297 194	180	0.61	0.52 to 0.70
During drug use	179 088	352	1.97	1.77 to 2.18	349 892	177	0.51	0.43 to 0.59
Duration								
<+30 days	16 266	120	7.38	6.12 to 8.82	33 324	33	0.99	0.68 to 1.39
31 to 60 days	15 367	43	2.80	2.03 to 3.77	30 162	16	0.53	0.30 to 0.86
61 to 90 days	14 877	29	1.95	1.31 to 2.80	28 913	12	0.42	0.21 to 0.72
91 to 180 days	37 955	60	1.58	1.21 to 2.03	73 920	27	0.37	0.24 to 0.53
181 to 270 days	32 398	40	1.23	0.88 to 1.68	63 084	24	0.38	0.24 to 0.57
271 to 360 days	26 760	27	1.01	0.67 to 1.47	52 588	22	0.42	0.26 to 0.63
>+360 days	35 465	33	0.93	0.64 to 1.31	67 901	45	0.66	0.48 to 0.89
After discontinuing use	46 892	40	0.85	0.61 to 1.16	91 164	51	0.56	0.42 to 0.74

Makani, H., Messerli, F. H., Romero, J., Wever-Pinzon, O., Korniyenko, A., Berrios, R. S., & Bangalore, S. (2012). Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. American Journal of Cardiology. https://doi.org/10.1016/j.amjcard.2012.03.034
Lewis, L. M. (2013). Angioedema: Etiology, pathophysiology, current and emerging therapies. Journal of Emergency Medicine. https://doi.org/10.1016/j.jemermed.2013.03.045
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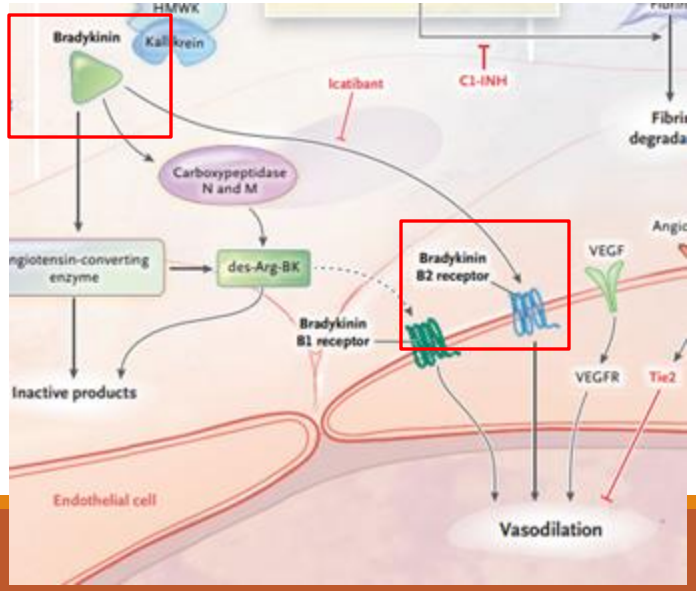
ACE-inhibitor Induced Angioedema

Treatment?

- STOP the ACEi!
- Supportive management
  - Maintain airway if needed
- No expected response to epinephrine, antihistamines, steroids!
- Icatibant (Firazyr)?
  - B2 receptor blocker



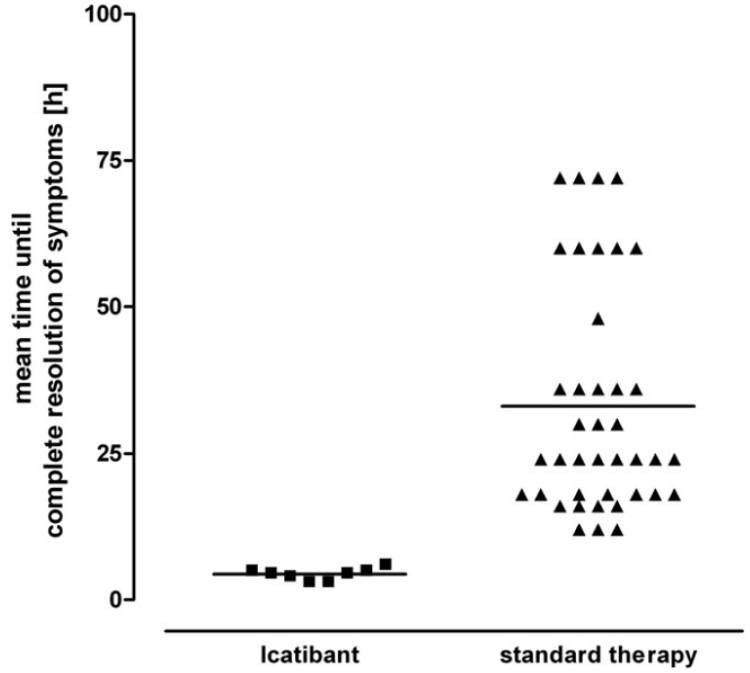


Figure 2. Mean time (hours) until complete resolution of symptoms in the 8 patients treated with icatibant and in a historical group of patients receiving standard therapy with methylprednisolone and clemastine.

TOXICOLOGY/BRIEF RESEARCH REPORT

Therapeutic Efficacy of Icatibant in Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors: A Case Series

Murat Bas, MD, Jens Greve, MD, Klaus Stelter, MD, Henning Bier, MD, Thomas Stark, MD, Thomas K. Hoffmann, MD, Georg Kojda, PharmD, PhD

From Hals-, Nasen- und Ohrenklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany (Bas, Bier, Stark); the Department of Otorhinolaryngology, University of Essen, Essen, Germany (Greve, Hoffmann); the Department of Otorhinolaryngology, University of Munich, Munich, Germany (Stelter); and the Institute of Pharmacology and Clinical Pharmacology, University of Duesseldorf, Dusseldorf, Germany (Kojda).

ACE-inhibitor Induced Angioedema

Icatibant (Firazyr)?

- B2 receptor blocker
- Subsequent studies have not shown significance…

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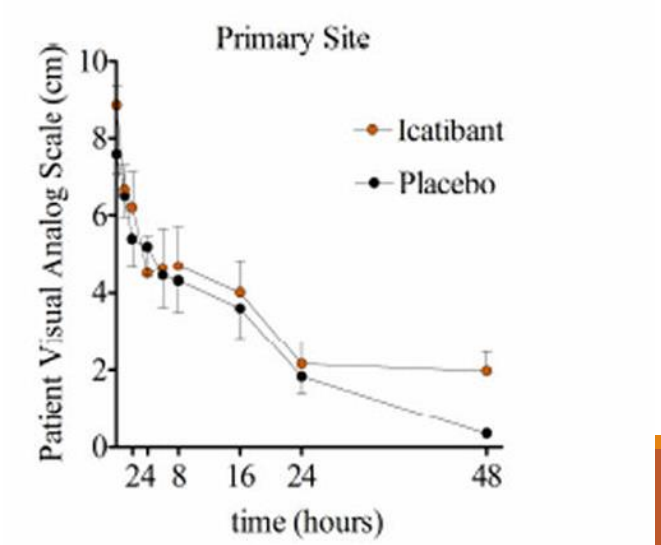
J Allergy Clin Immunol. 2017 July ; 140(1): 242–248.e2. doi:10.1016/j.jaci.2016.09.051.

Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema

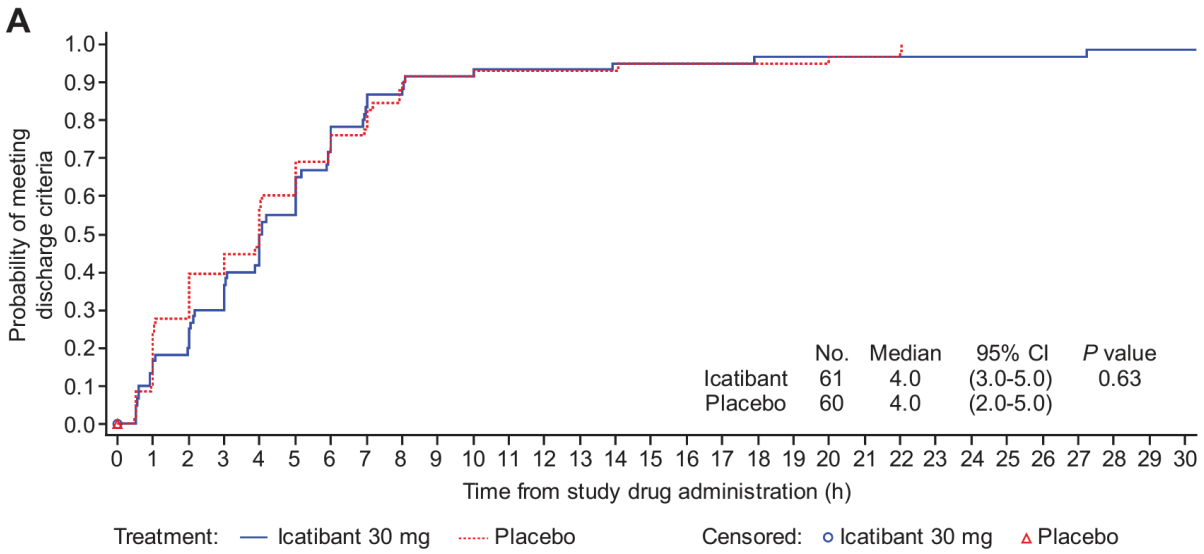
Brittany T. Straka, M.D.[1], Claudia E. Ramirez, M.D.[1], James B. Byrd, M.D., M.S.[1], Elizabeth Stone, R.N.[1], Alencia Woodard-Grice, Ph.D.[1], Hui Nian, M.S.[2], Chang Yu, Ph.D.[2], Aleena Banerji, M.D.[3], and Nancy J. Brown, M.D.[1]



Original Article

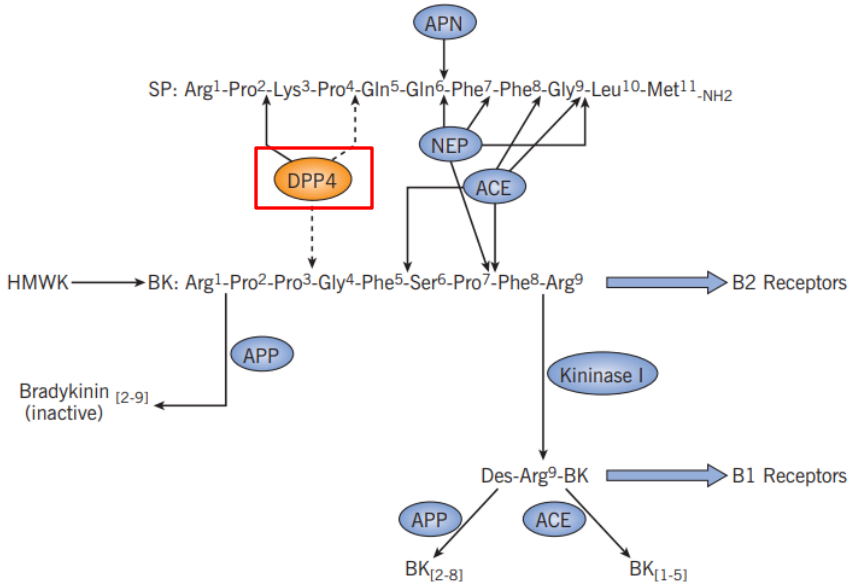
Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor–Induced Upper Airway Angioedema

Richard Sinert, DO[a], Phillip Levy, MD, MPH[b], Jonathan A. Bernstein, MD[c], Richard Body, MB ChB, PhD[d], Marco L.A. Sivilotti, MD, MSc[e], Joseph Moellman, MD[f], Jennifer Schranz, MD[g], Jovanna Baptista, MS[h], Alan Kimura, MD, PhD[g], and Wolfram Nothaft, MD[g]; on behalf of the CAMEO study group* *Brooklyn, NY; Detroit, Mich; Cincinnati, Ohio; Manchester, United Kingdom; Kingston, ON, Canada; and Lexington, Mass*



Drug-induced Angioedema

Degradation of bradykinin



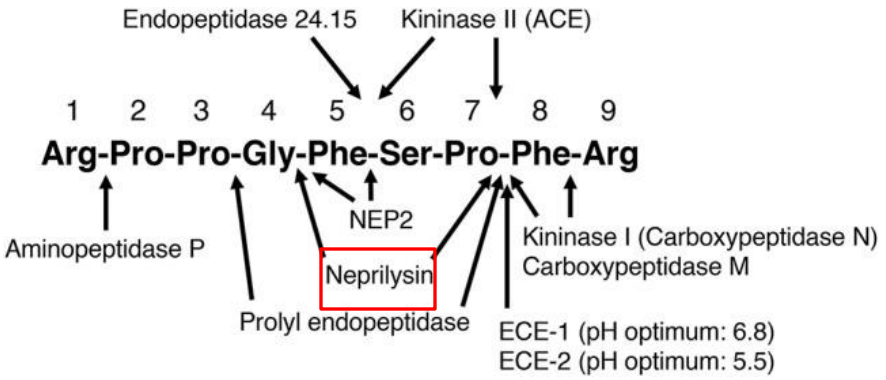


Fig. 12.6 Degradation of bradykinin, des-Arg9-bradykinin, and substance P. APN, aminopeptidase N or M; APP, aminopeptidase P; BK, bradykinin; DPP4, depeptidyl peptidase IV; HMWK, high-molecular-weight kininogen; NEP, neutral endopeptidase; SP, substance P. (From Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin N Am 2006; 26:725–737.)

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DPP-4 Inhibitors

Incidence and prevalence unknown

- Reports of angioedema, independently and with ACEi
  - Vildagliptin clinical trials data (n = 13921)
    - 19 cases of angioedema
    - 73% also taking ACEi
  - Treatment refractory angioedema
    - No regression >30 hrs, with C1-INH, icatibant, glucocorticoids

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 576-579
DOI: 10.12659/AJCR.901960

Drug-Induced Inhibition of Angiotensin Converting Enzyme and Dipeptidyl Peptidase 4 Results in Nearly Therapy Resistant Bradykinin Induced Angioedema: A Case Report

EF Janina Hahn
F Susanne Trainotti
A Thomas K. Hoffmann
AF Jens Greve

Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Ulm University Medical Center, Ulm-Michelsberg, Germany

Angiotensin-converting enzyme and dipeptidyl peptidase-4 inhibitor–induced angioedema: A disproportionality analysis of the WHO pharmacovigilance database

Marion Lepelley, PharmD[a], Charles Khouri, PharmD[a], Clémence Lacroix, PharmD[b], and Laurence Bouillet, PhD[c]

TABLE II. Disproportionality analysis of AE reports associating with ACEi and DPP-4i

Drugs	Cases (N)	Noncases (N)	ROR (95% CI)
ACEi	19,997	168,673	5.69 (5.61-5.78)
DPP-4i	677	71,233	0.43 (0.40-0.47)
ACEi + DPP-4i			
Details of DPP-4i– associated:	345	369	42.77 (36.93-49.53)
Sitagliptin	225	213	48.30 (40.05-58.26)
Linagliptin	37	55	30.75 (20.27-46.64)
Vildagliptin	40	30	60.94 (37.96-97.83)
Saxagliptin	43	102	19.27 (13.49-27.52)
Alogliptin	3	7	NA
Dihydropyridine CCBs	3,155	165,896	0.87 (0.84-0.90)
GLP-1 analogues	388	102,224	0.17 (0.16-0.19)

NA, Not available (due to number of cases being <5).

Neprilysin Inhibitors

Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study

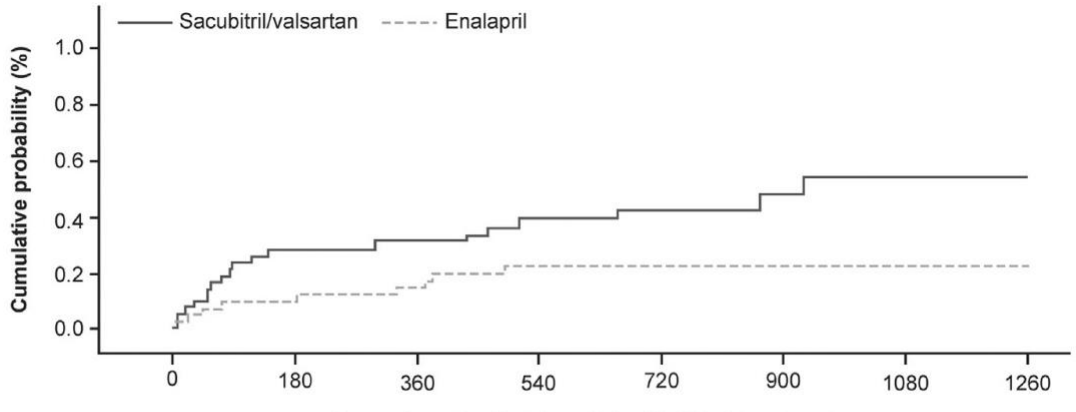
Victor Shi [a,*], Michele Senni [b], Hendrik Streefkerk [c], Vikas Modgill [c], Wenchun Zhou [a], Allen Kaplan [d]

During run-in period:

- Enalapril – 15 (0.14%)
- Sacubitril/valsartan – 10 (0.11%)

During double-blind phase:

- Enalapril – 10 (0.24%)
- Sacubitril/valsartan – 19 (0.45%)



Patients at risk

Sacubitril/valsartan	4203	4055	3888	3366	2534	1786	1069	336
Enalapril	4229	4058	3865	3301	2466	1793	1068	339

AAC, angioedema adjudication commitee

No significant difference in angioedema between enalapril and sacubitril/valsartan

tPA

Incidence – reported to be 0.2-5.1%

Mainly case reports

Typically orolingual angioedema

Can present with airway involvement

Treatment? Case reports of

- Icatibant
- FFP

CASE REPORT

Angioedema after thrombolysis with tissue plasminogen activator: an airway emergency

Kimberly M. Rathbun*

Case Report

Icatibant for the treatment of orolingual angioedema following the administration of tissue plasminogen activator☆

Emily Brown, PharmD [a], Christina Campana, DO [b,*], Jacob Zimmerman, PharmD BCCCP [a], Steven Brooks, MD [c]

Unilateral orolingual angioedema in a patient with sarcoidosis after intravenous thrombolysis due to acute stroke without improvement after treatment with icatibant

Anna Daniela Wollmach,[1] Daniel Zehnder,[2] Markus Schwendinger,[1] Alexander Andrea Tarnutzer [3,4]

Icatibant as a Potential Treatment of Life-Threatening Alteplase-Induced Angioedema

Edmund Cheong, MBBS, Lizzie Dodd, RN, William Smith, MBBS (Hons), PhD, FRACP, FRCPA, and Timothy Kleinig, MBBS (Hons), BA, PhD, FRACP

Angioedema after rt-PA infusion led to airway emergency: a case report of rescue treatment with fresh frozen plasma

Carlo Alberto Mazzoli [a,*], Maura Ida D'Angelo [a], Luigi Simonetti [b], Luigi Cirillo [c,d], Andrea Zini [e], Mauro Gentile [e], Giovanni Gordini [a], Carlo Coniglio [a]

Correia, A. S., Matias, G., Calado, S., Lourenço, A., & Viana-Baptista, M. (2015). Orolingual Angiodema Associated with Alteplase Treatment of Acute Stroke: A Reappraisal. Journal of Stroke and Cerebrovascular Diseases, 24(1), 31–40. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.07.045

Case 2

Swelling:
- Lip, tongue and throat
- Develops slowly over hours
- No overlying skin flaking or cracking
- Symptoms resolve over days

Associated symptoms:
- No abdominal pain, vomiting, dyspnea
- No rash

Treatment:
- Antihistamines ineffective

Potential triggers?
- No new foods, contacts, medications within 1 year

Medical History:
- Hypertension
- Type 2 Diabetes Mellitus

Medications:
- **Ramipril**
- Janumet (metformin/**sitagliptin**)
- Atorvastatin

What is the potential diagnosis?
- Drug-induced angioedema, like ACEi +/- DPP-4 inhibitor

What are treatment options?
- Discontinue the drugs!

Case 3

Claire is a 30 year-old woman who immigrated to Canada 1 year ago. She has had a history of swelling episodes since 12 years-old, occurring 3-4 times per year. Bumps on the skin can cause an episode of swelling that would last for 3 days.

What additional info would you like?

Case 3

Swelling:
- Skin – face, limbs, genitals
- 1 episode of throat tightness
  - Stayed in a hospital in Philippines for 1 week

Associated symptoms:
- No rash
- Episodes of debilitating abdominal pain 1/year, requiring time off work

Treatment:
- Tried transfusions in Philippines and ineffective

Potential triggers?
- Can occur randomly

Medical History:
- Otherwise healthy

Medications:
- None

Family History:
- Mother passed away from a throat swelling attack
- 2 sons – 1 in Canada

What is the potential diagnosis?

What are treatment options?

Case 3

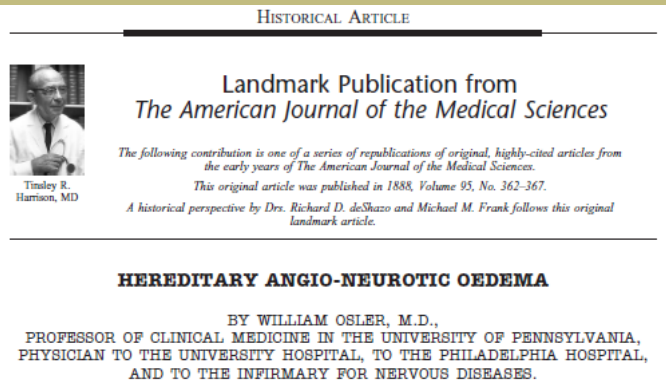
Investigations?

- C1-INH function – 0.17 (0.7 – 1.3)
- C4 – 0.03 (0.09 – 0.5)
- C1-INH level – 43mg/L (210 - 390)
  - From 2017, Philippines

What is the diagnosis?

Hereditary Angioedema

1888: First described as angioneurotic edema by Sir William Osler



HISTORICAL ARTICLE

Tinsley R. Harrison, MD

Landmark Publication from
The American Journal of the Medical Sciences

The following contribution is one of a series of republications of original, highly-cited articles from the early years of The American Journal of the Medical Sciences.

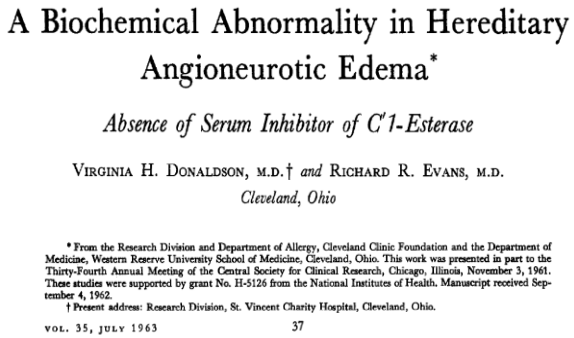
This original article was published in 1888, Volume 95, No. 362–367.

A historical perspective by Drs. Richard D. deShazo and Michael M. Frank follows this original landmark article.

HEREDITARY ANGIO-NEUROTIC OEDEMA

BY WILLIAM OSLER, M.D.,
PROFESSOR OF CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA,
PHYSICIAN TO THE UNIVERSITY HOSPITAL, TO THE PHILADELPHIA HOSPITAL,
AND TO THE INFIRMARY FOR NERVOUS DISEASES.

1963: C1-INH deficiency as etiology noted by Donaldson and Evans



A Biochemical Abnormality in Hereditary Angioneurotic Edema*

Absence of Serum Inhibitor of C'1-Esterase

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VOL. 35, JULY 1963 37

HAE is a rare autosomal dominant disorder resulting from C1-INH deficiency[1,2]

- Reduced activity of C1-INH may result in elevated levels of bradykinin[3,4]

Characterized by recurrent episodes of localized subcutaneous or mucosal swelling[1,2]

- Bradykinin is the key mediator of symptoms (pain, swelling) in HAE[3,4]

Angioedema attacks are often painful, debilitating and sometimes life-threatening[2]

C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema

1. Lumry WR. *Am J Manag Care*. 2013;19:S111–S118; 2. Lumry WR. *Am J Manag Care*. 2013;19:S103–S110; 3. Cicardi M. *NEJM*. 2010;363:532–541; 4. Lumry WR. *Ann Allergy Asthma Immunol*. 2011;107:529–37

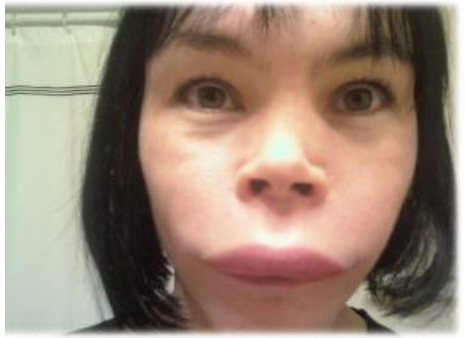
Presentation

Cutaneous attacks

Abdominal attacks

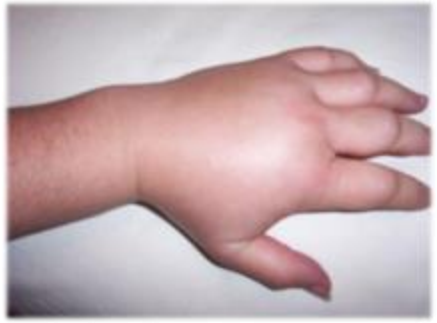
Laryngeal attacks

Pre-facial swelling

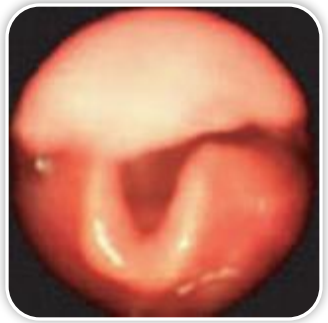


Facial swelling

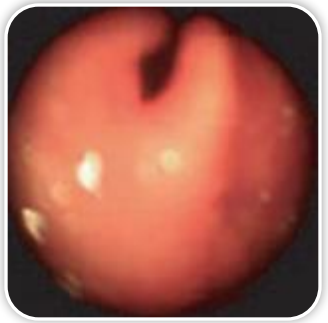
US Hereditary Angioedema Association
www.haeimages.com



US Hereditary Angioedema Association.
www.haeimages.com.



Pre-laryngeal swelling



Laryngeal swelling

http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2006.01197.x/epdf

Abdominal swelling

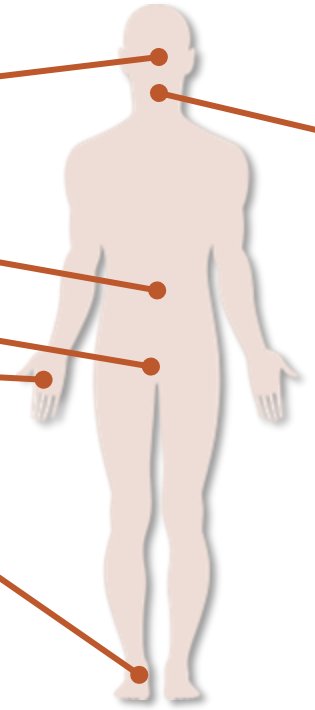
Post-abdominal swelling

US Hereditary Angioedema Association
www.haeimages.com

Angioedema attacks vary in location, frequency, duration, and severity[3,4]

Most common locations:[3–6]

- Face
- Abdominal
- Urogenital
- Extremities



Less common:[3]

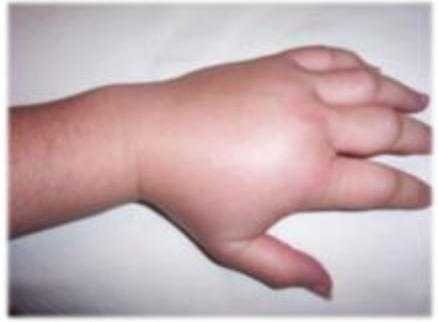
- Laryngeal
  - 50% of patients will have at ≥1 laryngeal attack in their lifetime[6,7]
  - Death may result due to airway obstruction and asphyxiation[3,6,7]
  - Asphyxia may ensue more rapidly in children than adults[6]

HAE, hereditary angioedema

1. Zuraw BL. *N Engl J Med*. 2008;359:1027–36; 2. Nzeako UC, *et al. Arch Intern Med*. 2001;161:2417–29; 3. Lumry WR. *Am J Manag Care*. 2013;19:S111–S118; 4. Farkas H. *Allergy Asthma Clin Immunol*. 2010;6:18; 5. Nygren A, *et al. Acta Paediatr*. 2016;105:529–34; 6. Lumry WR. *Am J Manag Care*. 2013;19:S103–S110; 7. Agostoni A, *et al. J Allergy Clin Immunol*. 2004;114(3 suppl):S51–S131

Cutaneous attacks

- Cutaneous edema (upper image) is a common, disfiguring and disabling symptom of HAE[1]
- Patients may first notice a sensation of tingling prior to the start of skin swelling[2–4]
- Some patients have an erythematous, nonpruritic, nonraised rash, known as erythema marginatum (lower image)[1–4]
- Angioedema develops over several hours[4]
- Swelling can interfere with daily functioning (e.g., inability to dress or wear shoes)[5]
- Angioedema usually resolves in 2–5 days, but may last longer[4,6,7]



US Hereditary Angioedema Association. www.haeimages.com.

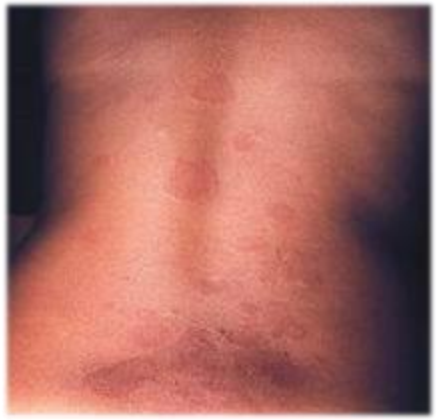


Image from Binotto MS, *et al. Images Paediatr Cardiol.* 2002;11:12–31

HAE, hereditary angioedema

1. Frank MM. eMedicine. September 2010. http://www.emedicine.com/med/topic420.htm; 2. Frank MM. *Immunol Allergy Clin North Am*. 2006;26:653–68; 3. MacGinnitie AJ. *Pediatr Allergy Immunol*. 2014;25:420–7; 4. Zuraw BL. *N Engl J Med*. 2008;359:1027–36; 5. Lumry WR, *et al. Allergy Asthma Proc*. 2010;31:407–14; 6. Wilson DA, *et al. Ann Allergy Asthma Immunol*. 2010;104:314–20; 7. Agostoni A, *et al. J Allergy Clin Immunol*. 2004;114(3 suppl):S51–S131

Abdominal attacks

Abdominal pain is caused by edema of the mucosa at any portion of the GI tract[1]

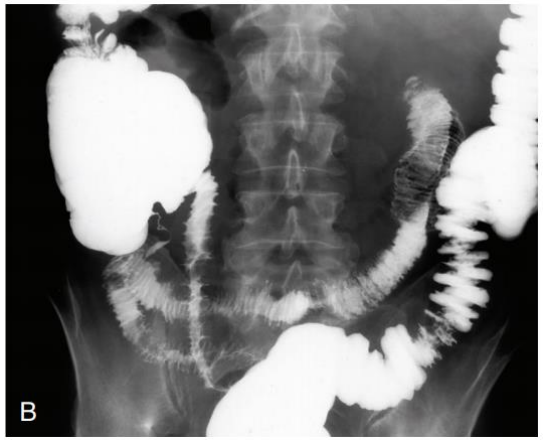
Abdominal pain can be severe and may lead to unnecessary surgeries[1,2]

Abdominal attacks are often accompanied by vomiting and/or diarrhea[3]

Abdominal films, CT scans, ultrasonography, or endoscopy may be useful in identifying edema of the intestinal wall[1,4,5]

Abdominal swelling *Post-abdominal swelling*

US Hereditary Angioedema Association
www.haeimages.com



Abdominal attacks are common, occurring in ~70–80% of patients with HAE[5]

- Patients report needing 24–50 hours of bed rest per attack[3]
- Abdominal attacks may necessitate hospitalization[3]

CT, computed tomography; GI, gastrointestinal; HAE, hereditary angioedema

1. Frank MM. eMedicine. September 2010. http://www.emedicine.com/med/topic420.htm; 2. Frank MM. *Immunol Allergy Clin North Am*. 2006;26:653–68; 3. Bork K, *et al. Am J Gastroenterol*. 2006;101:619–27; 4. Koruth JS, *et al. Gastrointest Endosc*. 2005;61:907–11; 5. Agostoni A, *et al. J Allergy Clin Immunol*. 2004;114(3 suppl):S51–S131

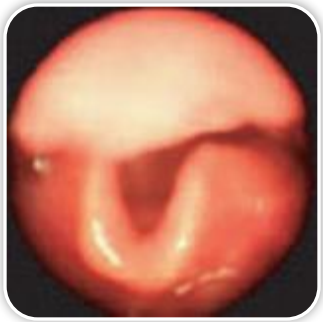
Laryngeal attacks

Laryngeal attacks are rare…

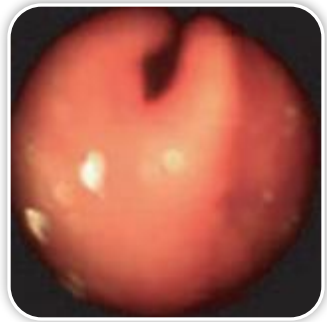
- In a retrospective analysis of 131,110 attacks in 209 patients with HAE due to
  C1-INH deficiency:
  - 0.9% of attacks affected the larynx
  - ~50% of patients had experienced at least one laryngeal attack at some point in their lives

… But can be life threatening: Asphyxiation can occur as little as 20 min after the onset of laryngeal symptoms

Bork K, *et al. Am J Med*. 2006;119:267–74



Pre-laryngeal swelling



Laryngeal swelling

http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2006.01197.x/epdf

Triggers?

- Attacks are sometimes, but not always, associated w/ triggers
- Onset of attack can be hours after the trigger
  - Bork et al 2011 – Onset of HAE attack average 14.3 hours after tooth extraction

Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study

Konrad Bork, MD,[a] Jochen Hardt, PhD,[b] Petra Staubach-Renz, MD,[a] and Guenther Witzke, PhD,[a] Mainz, Germany
JOHANNES GUTENBERG UNIVERSITY

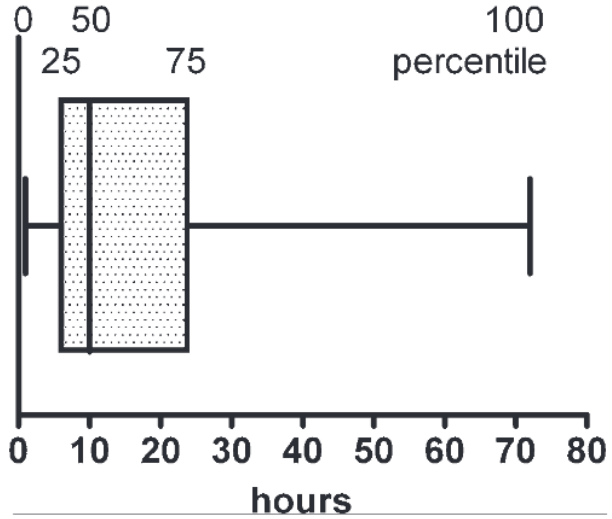


Fig. 3. Reported time lag between tooth extraction and onset of hereditary angioedema symptoms in 124 tooth extractions without prophylaxis (box plot).

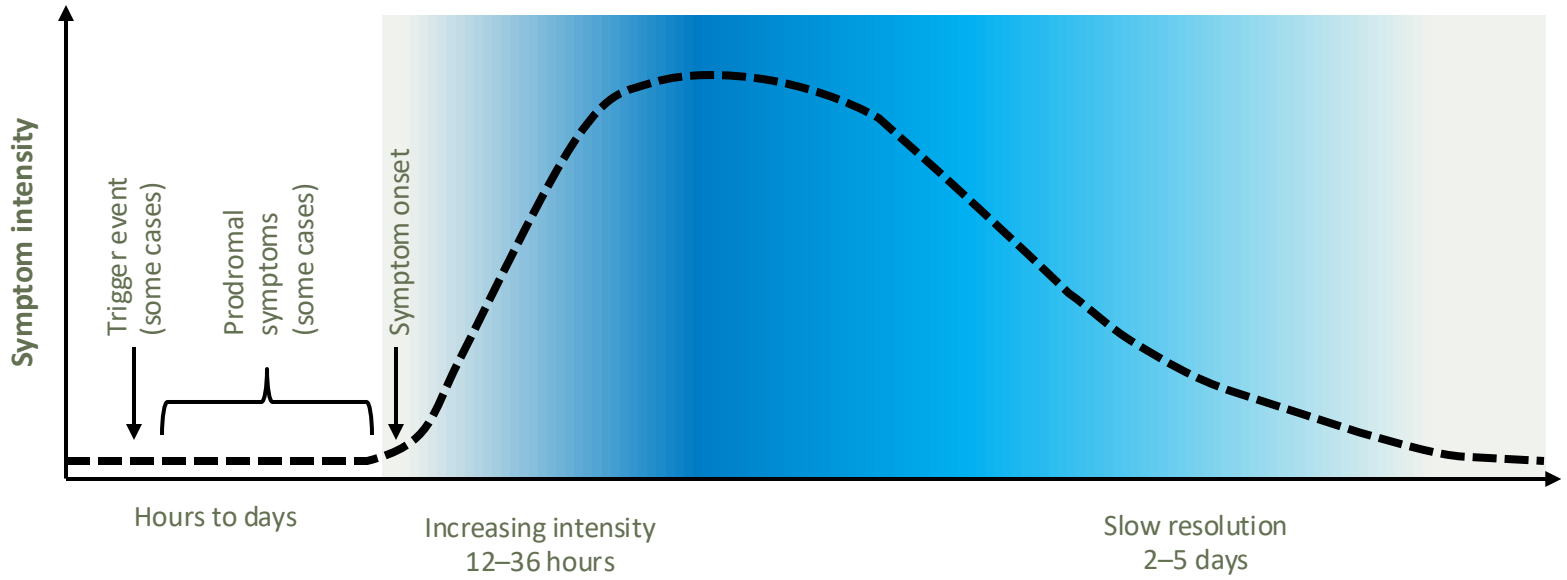
https://www.berinert.com/patients/support-services/what-is-hae

Presentation

Symptoms typically worsen over the first 24 hours and subside over the next 48–72 hours[1]

- Attacks can last up to 5 days[2] and may spread to another location before resolving[1]

Course of a typical untreated HAE attack[1–3]



HAE, hereditary angioedema

1. Zuraw BL. *N Engl J Med*. 2008;359:1027–36; 2. MacGinnitie AJ. *Pediatr Allergy Immunol*. 2014;25:420–7; 3. Banerji A, *et al. Ann Allergy Asthma Immunol*. 2013;111:329–36

Epidemiology

- Inheritance pattern
  - Autosomal dominant
  - 25% *de novo* mutation
- Mean age of onset: 8-12 years
- Average delay in diagnosis: 8 years

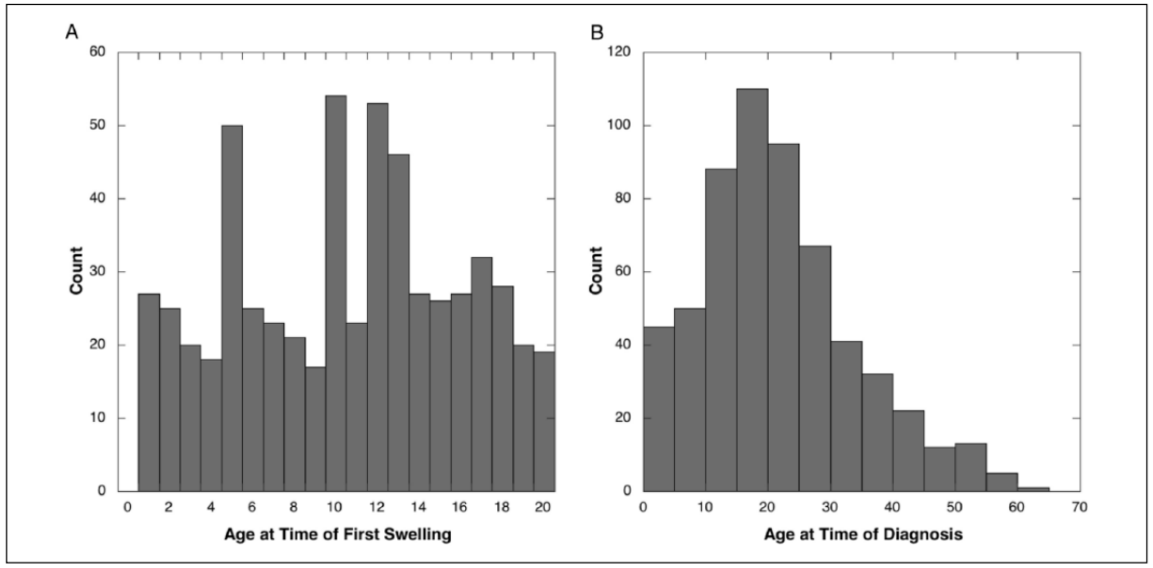
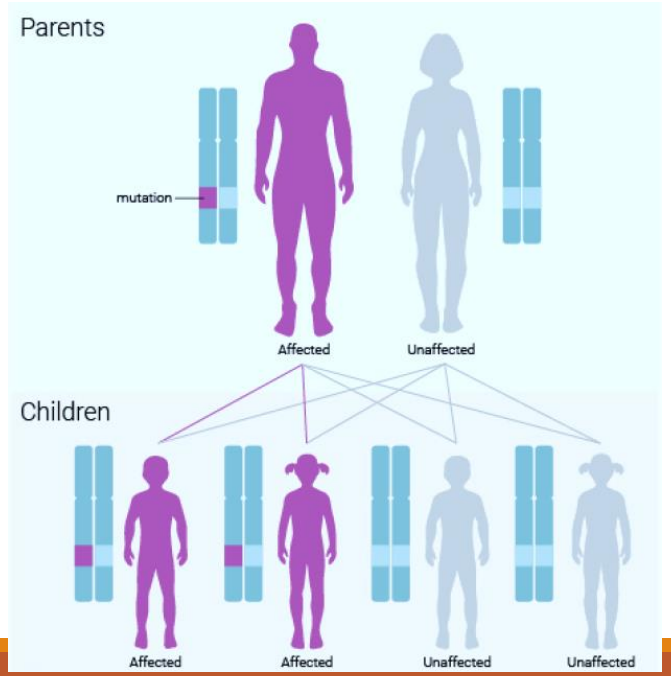


Figure 1. Histograms of age of swelling onset and diagnosis in 581 patients with hereditary angioedema (HAE). (A) Number of subjects who reported onset of swelling from ages 1 to 20 years. (B) Reported age of HAE diagnosis.

Autosomal dominant inheritance[8]



Christiansen, S. C., Davis, D. K., Castaldo, A. J., & Zuraw, B. L. (2016). Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. Clinical Pediatrics. https://doi.org/10.1177/0009922815616886

Epidemiology

- 1:50,000
- Population of Lower Mainland – 2,966,830 – 59 patients expected

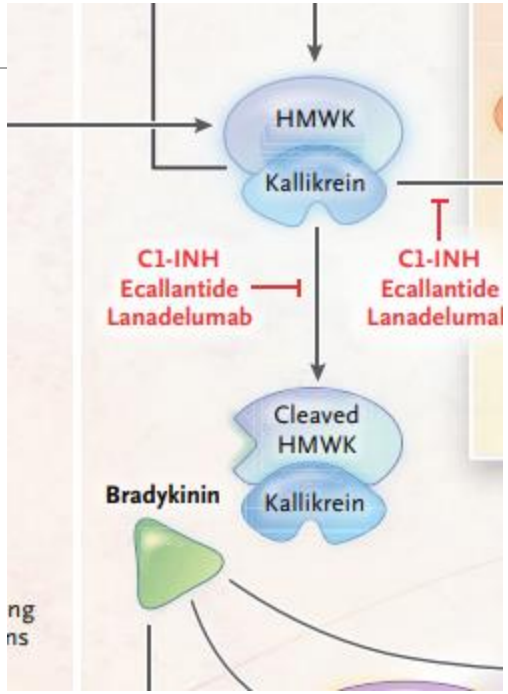
Christiansen, S. C., Davis, D. K., Castaldo, A. J., & Zuraw, B. L. (2016). Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. Clinical Pediatrics. https://doi.org/10.1177/0009922815616886

Pathophysiology

Where does bradykinin come from?

Kallikrein-Kinin system

- High Molecular Weight Kininogen
  - Chromosome 3q35
  - 6 domains
    - Domain 4 contains bradykinin sequence
    - Domain 5 involved in coagulation
- Kallikrein
  - Activated from pre-kallikrein with binding to endothelium
  - Chromosome 4q34-35



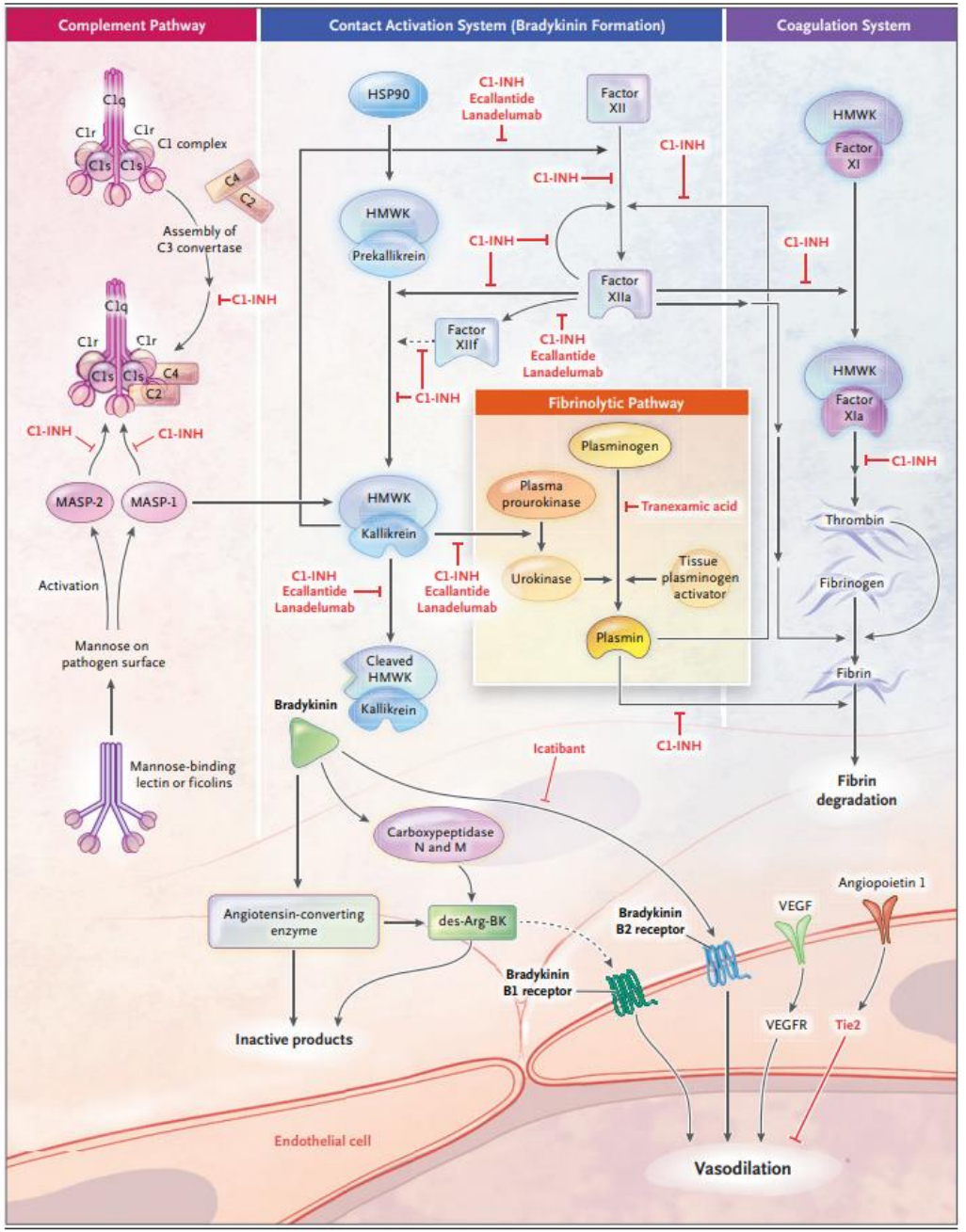
Busse, P. J., & Christiansen, S. C. (2020). Hereditary Angioedema. The New England Journal of Medicine, 382, 1136–1148.

C1 Inhibitor

Serine protease inhibitor

Traps target protease when cleaved
- “mousetrap”
- “suicide inhibitor”

Dysfunction or depletion leads to pathology
- Hereditary angioedema type I, II
- Acquired angioedema

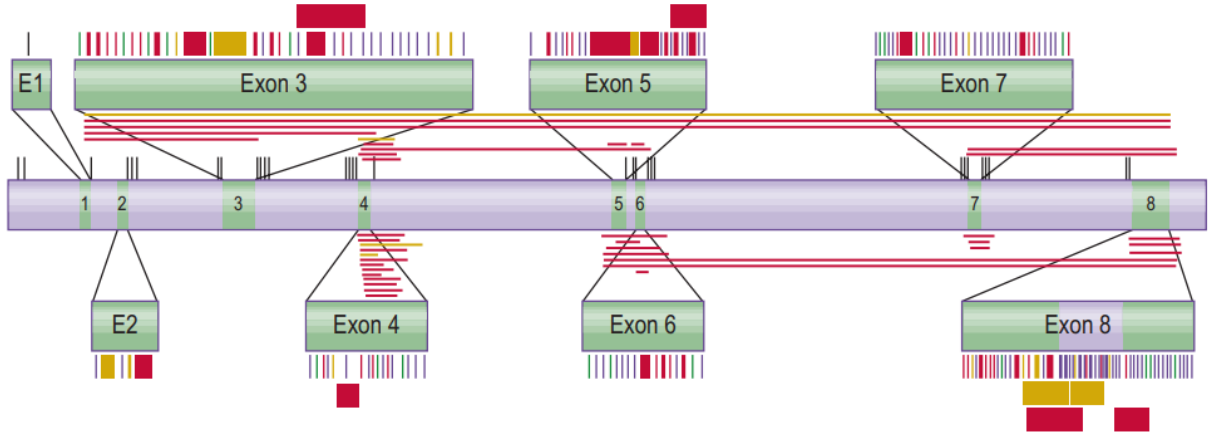


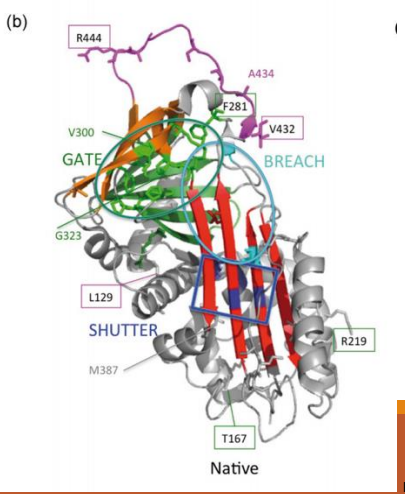
Busse, P. J., & Christiansen, S. C. (2020). Hereditary Angioedema. The New England Journal of Medicine, 382, 1136–1148.

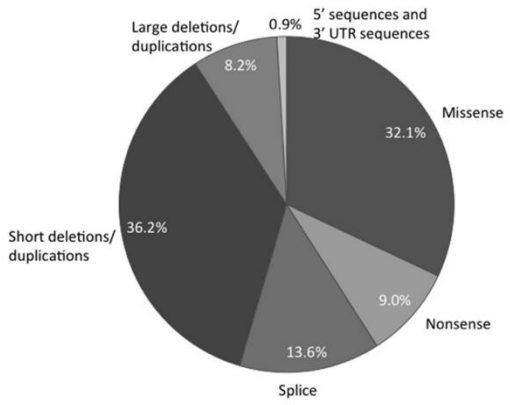
Hereditary Angioedema

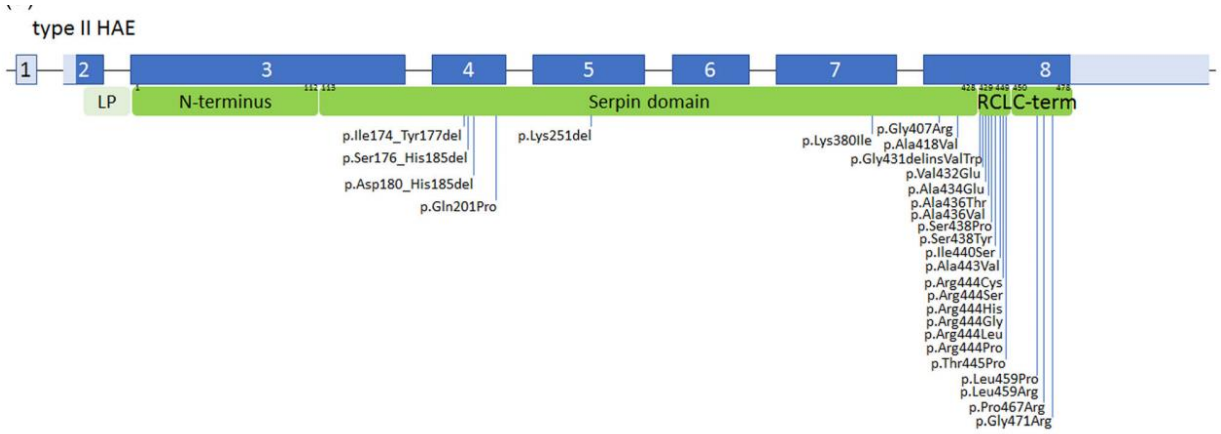
HAE-C1-INH

- SERPING1 gene
  - Over 700 published variants
- Autosomal dominant
  - C1-INH function generally 5-30%
  - 40% C1-INH function needed to prevent attacks









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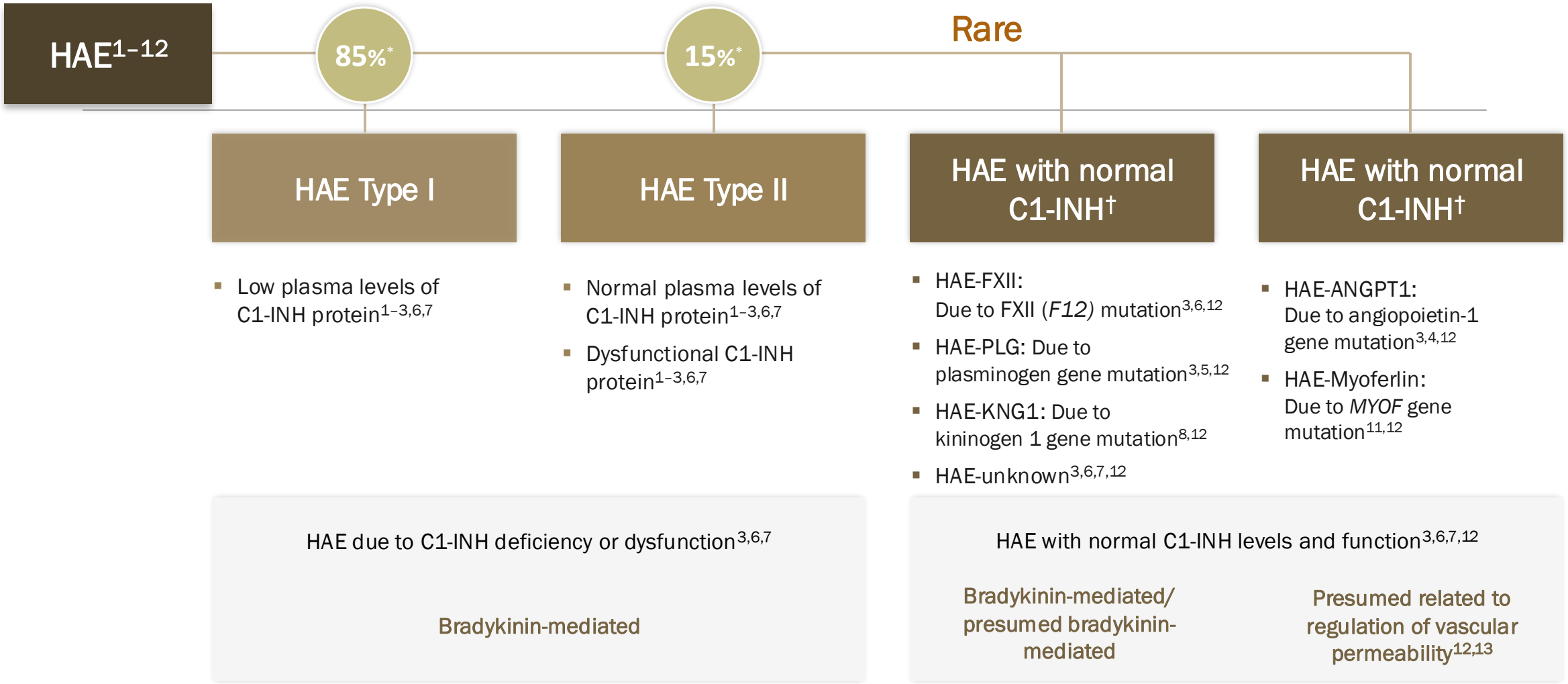
Ponard, D., Gaboriaud, C., Charignon, D., Ghannam, A., Wagenaar-Bos, I. G. A., Roem, D., ... Drouet, C. (2020). SERPING1 mutation update: Mutation spectrum and C1 Inhibitor phenotypes. Human Mutation. https://doi.org/10.1002/humu.23917

Longhurst, H., Cicardi, M., Craig, T., Bork, K., Grattan, C., Baker, J., ... Zuraw, B. L. (2017). Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. New England Journal of Medicine https://doi.org/10.1056/nejmoa1613627

Types of HAE



*In Chinese patients, HAE-1 and HAE-2 account for 98.7% and 1.3% of cases, respectively[9]
†Previously referred to as 'Type III'[3,6,10]
C1-INH, C1 esterase inhibitor; FXII, factor XII (also known as F12); HAE, hereditary angioedema; HAE-ANGPT1, HAE with an angiopoietin-1 gene mutation; HAE-FXII, HAE with a known F12 mutation; HAE-KNG1, HAE with a mutation in the kininogen 1 gene; HAE-PLG, HAE with a mutation in the plasminogen gene; MYOF, myoferlin

1. Lumry WR. *Am J Manag Care*. 2013;19(7 Suppl):S103–S110; 2. Zuraw BL. *N Engl J Med*. 2008;359(10):1027-1036; 3. Zuraw BL. *J Allergy Clin Immunol*. 2018;141(3):884-885; 4. Bafunno V, et al. *J Allergy Clin Immunol*. 2018;141(3):1009-1017; 5. Bork K, et al. *Allergy*. 2018;73(2):442-450; 6. Cicardi M, et al. *Allergy*. 2014;69(5):602-616; 7. Longhurst HJ, Bork K. *Br J Hosp Med*. 2019;80(7):391-398; 8. Bork K, et al. *Allergy*. 2019;74(12):2479-2481; 9. Liu S, et al. *Eur J Dermatol*. 2019;29(1):14–20; 10. Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3; 11. Ariano A, et al. *Allergy*. 2020;75(11):2989-2992; 12. Bork K, et al. *Orphanet J Rare Dis*. 2020;15(1):289; 13. Banday AZ, et al. *Genes & Diseases*. 2020;7(1):75–83.

Why is it called C1 inhibitor anyway?

- C1 INH inhibits C1s in classical pathway of complement system
- Reduced C1 INH means MORE C1 activity
- MORE C4 get cleaved
- C4 levels are reduced

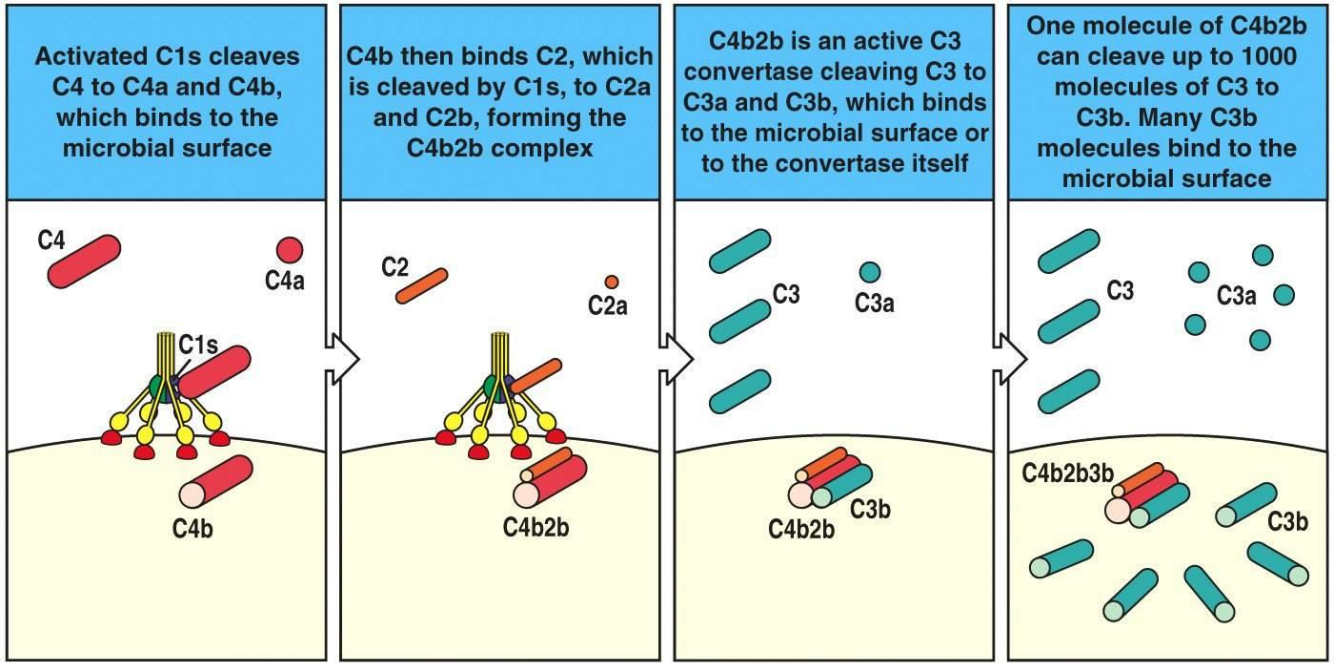


Figure 2-22 Immunobiology, 6/e. (© Garland Science 2005)

Busse, P. J., & Christiansen, S. C. (2020). Hereditary Angioedema. The New England Journal of Medicine, 382, 1136–1148.

Investigations?

Diagnosis:

- Compatible history
- Consistent laboratory findings
  - Caution with C4 in children <1 year

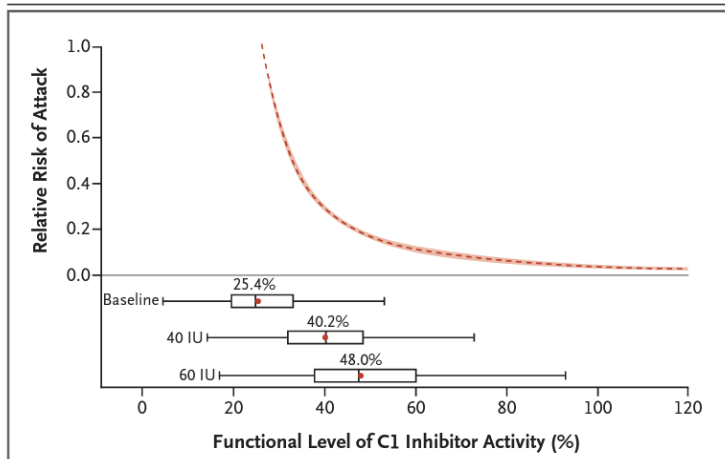


Figure 2. Relationship between Functional Levels of C1 Inhibitor Activity and the Relative Risk of an Attack of Hereditary Angioedema.

Table 1 Laboratory findings in hereditary angioedema [9–11]

Function	C4	C1-INH antigen	C1-INH
HAE-1	↓	↓	↓
HAE-2	↓	normal or ↑	↓
HAE-nC1INH variants coagulation factor XII angiopoietin-1 plasminogen unknown	normal	normal	normal

Canadian guideline

Diagnosis of HAE

1. The diagnosis of HAE-1/2 should be made by measuring plasma levels of C4, C1-INH antigen and, when necessary, C1-INH function	High, Strong
2. All individuals with a positive family history should be considered to be at risk of HAE and should be screened as early as possible	Consensus, Strong

Betschel, S., Badiou, J., Binkley, K., Borici-Mazi, R., Hébert, J., Kanani, A., ... Tsai, E. (2019). The International/Canadian Hereditary Angioedema Guideline. Allergy, Asthma and Clinical Immunology. https://doi.org/10.1186/s13223-019-0376-8

Measuring AgC1-INH, fC1-INH, C4 and C1q are Critical to Inform Angioedema Diagnosis

Diagnostic laboratory profile of non-histaminergic angioedema phenotypes[1–7]

Type		Family history: yes (hereditary); no (acquired)	Biochemical tests				Genetic tests				
			AgC1-INH level	fC1-INH level	C4 level	C1q level	C1-INH mutation	FXII mutation	ANGPT1 mutation	PLG mutation	KNG1 mutation
HAE Type I		Yes	↓	↓	↓	Normal	Yes	No	No	No	No
HAE Type II		Yes	Normal or ↑	↓	↓	Normal	Yes	No	No	No	No
HAE-nC1-INH	HAE-FXII	Yes	Normal	Normal	Normal	Normal	No	Yes	No	No	No
	HAE-ANGPT1	Yes	Normal	Normal	Normal	Normal	No	No	Yes	No	No
	HAE-PLG	Yes	Normal	Normal	Normal	Normal	No	No	No	Yes	No
	HAE-KNG1	Yes	Normal	Normal	Normal	Normal	No	No	No	No	Yes
	HAE-UNK	Yes	Normal	Normal	Normal	Normal	No	No	No	No	No
C1-INH-AAE		No	↓ or normal	↓	↓	↓	No	No	No	No	No
InH-AAE		No	Normal	Normal	Normal	Normal	No	No	No	No	No

AAE, acquired angioedema; AgC1-INH, antigenic C1 esterase inhibitor; ANGPT1, angiopoietin 1; C1-INH, C1 esterase inhibitor; C1q, complement component 1q; C4, complement component 4; fC1-INH, functional C1 esterase inhibitor; FXII, FXII, factor XII (also known as F12); HAE, hereditary angioedema; HAE-ANGPT1, HAE with ANGPT1 mutation; HAE-nC1-INH, HAE with normal C1 esterase inhibitor levels HAE-KNG1; HAE with KNG1 mutation; HAE-PLG, HAE with PLG mutation; HAE-UNK, HAE with unknown mutation; InH-AAE, idiopathic non-histaminergic acquired angioedema; KNG1, kininogen 1; PLG, plasminogen

1. Farkas H, et al. *Clinic Rev Allergy Immunol*. 2016;51(2):140-151; 2. Zuraw BL, Christiansen SC. *Allergy Asthma Proc*. 2009;30(5):487-492; 3. Nzeako UC, et al. *Arch Intern Med*. 2001;161(20):2417-2429; 4. Maurer M, et al. *Allergy*. 2018;73(8):1575-1596; 5. Zuraw BL. *J Allergy Clin Immunol*. 2018;141(3):884-885; 6. Bork K, et al. *Allergy*. 2019;74(12):2479-2481; 7. Caballero T, et al. *J Invest Allergol Clin Immunol*. 2011;21(5):333-347.

Management Approach

1. Trigger avoidance
2. On-demand therapy
3. Short-term prophylaxis
4. Long-term prophylaxis
5. Genetic counselling

Betschel *et al.*
Allergy Asthma Clin Immunol (2019) 15:72
https://doi.org/10.1186/s13223-019-0376-8

Allergy, Asthma & Clinical Immunology

REVIEW Open Access

The International/Canadian Hereditary Angioedema Guideline

Stephen Betschel[1*], Jacquie Badiou[2], Karen Binkley[1], Rozita Borici-Mazi[3], Jacques Hébert[4], Amin Kanani[5], Paul Keith[6], Gina Lacuesta[7], Susan Waserman[6], Bill Yang[8], Emel Aygören-Pürsün[9], Jonathan Bernstein[10], Konrad Bork[11], Teresa Caballero[12], Marco Cicardi[13], Timothy Craig[14], Henriette Farkas[15], Anete Grumach[16], Connie Katelaris[17], Hilary Longhurst[18], Marc Riedl[19], Bruce Zuraw[19], Magdelena Berger[20], Jean-Nicolas Boursiquot[21], Henrik Boysen[22], Anthony Castaldo[23], Hugo Chapdelaine[24], Lori Connors[7], Lisa Fu[25], Dawn Goodyear[26], Alison Haynes[27], Palinder Kamra[28], Harold Kim[29,30], Kelly Lang-Robertson[1], Eric Leith[31], Christine McCusker[32], Bill Moote[33], Andrew O'Keefe[27], Ibraheem Othman[34], Man-Chiu Poon[35], Bruce Ritchie[36], Charles St-Pierre[37], Donald Stark[38] and Ellie Tsai[39]

Triggers?

- Attacks are sometimes, but not always, associated w/ triggers
- Onset of attack can be hours after the trigger
  - Bork et al 2011 – Onset of HAE attack average 14.3 hours after tooth extraction

Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study

Konrad Bork, MD,[a] Jochen Hardt, PhD,[b] Petra Staubach-Renz, MD,[a] and Guenther Witzke, PhD,[a] Mainz, Germany
JOHANNES GUTENBERG UNIVERSITY

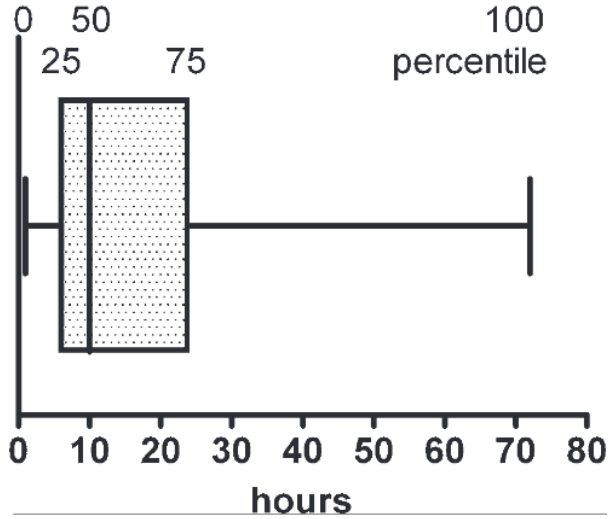


Fig. 3. Reported time lag between tooth extraction and onset of hereditary angioedema symptoms in 124 tooth extractions without prophylaxis (box plot).

https://www.berinert.com/patients/support-services/what-is-hae

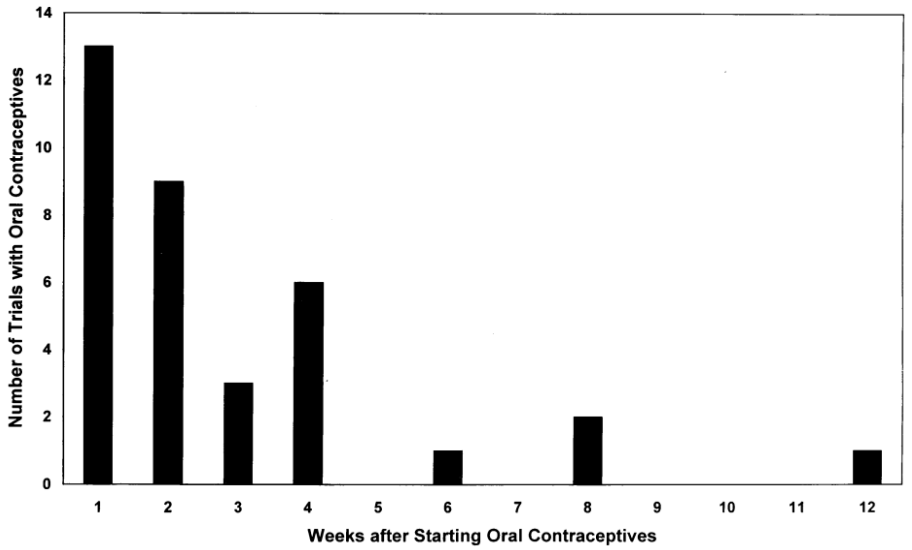
Hereditary Angioedema

Trigger medications

- Estrogen-containing OCP
- Previously discussed medications
  - ACEi inhibitor
  - DPP-4 inhibitor
  - Neprilysin inhibitor

Recurrent Episodes of Skin Angioedema and Severe Attacks of Abdominal Pain Induced by Oral Contraceptives or Hormone Replacement Therapy

Konrad Bork, MD, Bettina Fischer, MD, Georg Dewald, MD



Management Approach

1. Trigger avoidance
2. **On-demand therapy**
3. Short-term prophylaxis
4. Long-term prophylaxis
5. Genetic counselling

Betschel *et al.*
Allergy Asthma Clin Immunol (2019) 15:72
https://doi.org/10.1186/s13223-019-0376-8

Allergy, Asthma & Clinical Immunology

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On-demand treatment

Note the timing of treatment effect

Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency

Konrad Bork, MD,[a] Jochen Hardt, PhD,[b] and Günther Witzke, PhD[a] *Mainz, Germany*

FIG 4. Mean durations of the 3 phases of fatal laryngeal attacks in 36 patients with HAE-C1-INH.

Phase 1 – Predyspnea
Phase 2 – Dyspnea until loss of consciousness
Phase 3 – LoC until cessation of breathing and loss of pulse

On-demand treatment

Options?

- YES!
  - C1-INH (Berinert, Cinryze, Rucorest)
  - Icatibant (Firazyr)
  - Ecallantide (Not available in Canada)
- Only if no other options
  - Fresh Frozen Plasma
- NO!
  - Attenuated androgens (e.g. Danazol)
  - Tranexamic acid

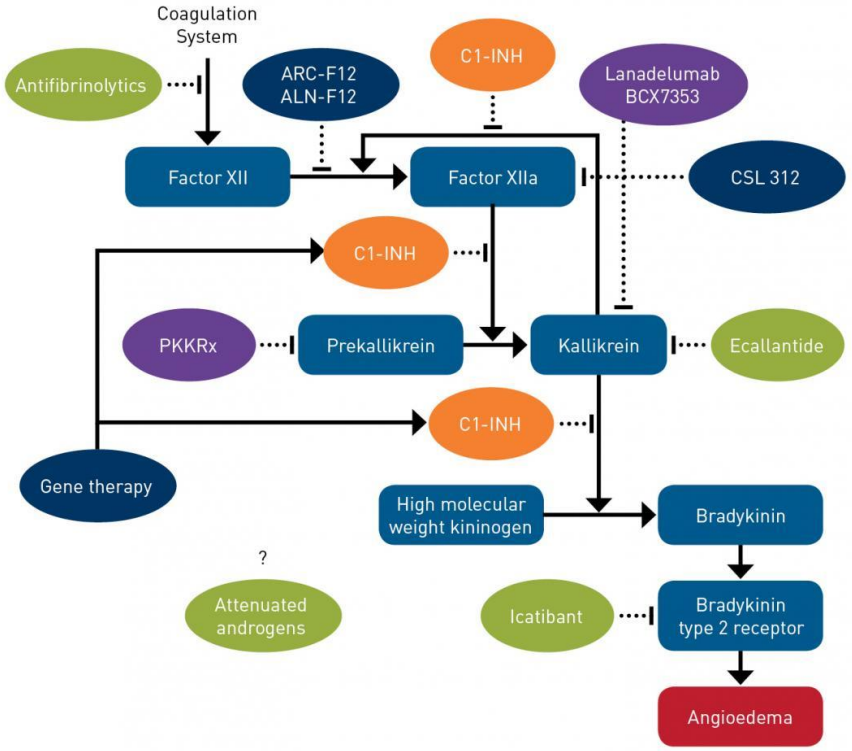
4. Intravenous pdC1-INH is an effective therapy for the acute treatment of attacks	High, Strong
5. Icatibant is an effective therapy for the acute treatment of attacks	High, Strong
6. Ecallantide is an effective therapy for the acute treatment of attacks	High, Strong
7. Intravenous rhC1-INH is an effective therapy for the acute treatment of attacks	High, Strong
8. Attenuated androgens should not be used for the acute treatment of attacks	Low, Strong
9. Tranexamic acid should not be used for the acute treatment of attacks	Low, Strong
10. Frozen plasma could be used for acute treatment of attacks if other recommended therapies are not available	Low, Strong

On-demand treatment

Options?

- YES!
  - C1-INH (Berinert, Cinryze, Rucorest)
  - Icatibant (Firazyr)
  - Ecallantide (Not available in Canada)
- Only if no other options
  - Fresh Frozen Plasma
- NO!
  - Attenuated androgens (e.g. Danazol)
  - Tranexamic acid

FIGURE 2. Emerging Treatment Options for HAE[2,6,7]

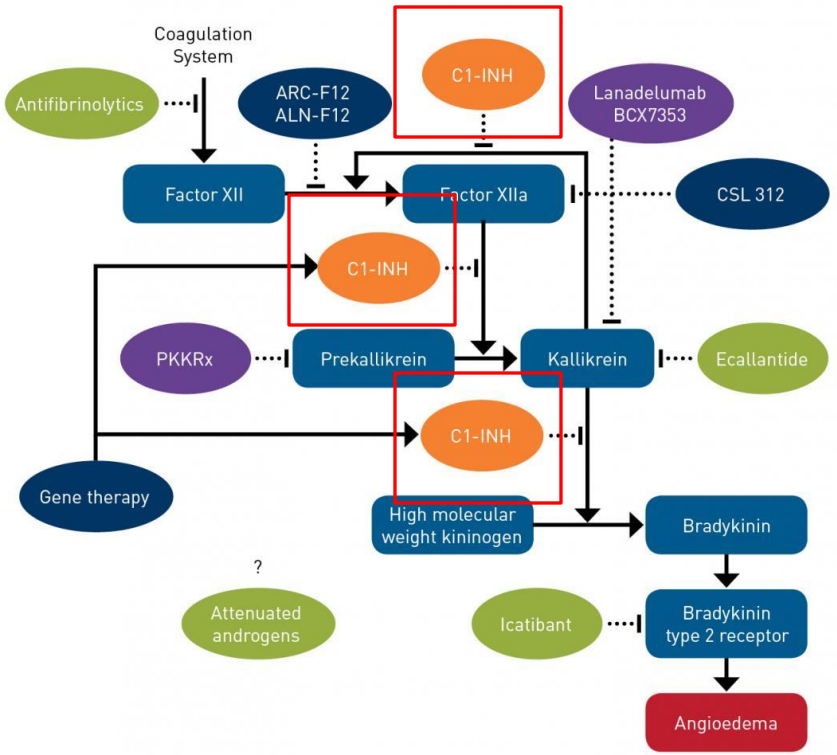


C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

On-demand treatment

- pdC1-INH replacement 20 U/kg **IV** (Berinert)
  - Covered by blood bank
- icatibant **subcut** (Firazyr)

FIGURE 2. Emerging Treatment Options for HAE[2,6,7]



C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

On-demand treatment

- pdC1-INH replacement 20 U/kg **IV** (Berinert)
  - Covered by blood bank
  - Patient support program available
  - Nurse will visit patient to provide training
- icatibant **subcut** (Firazyr)

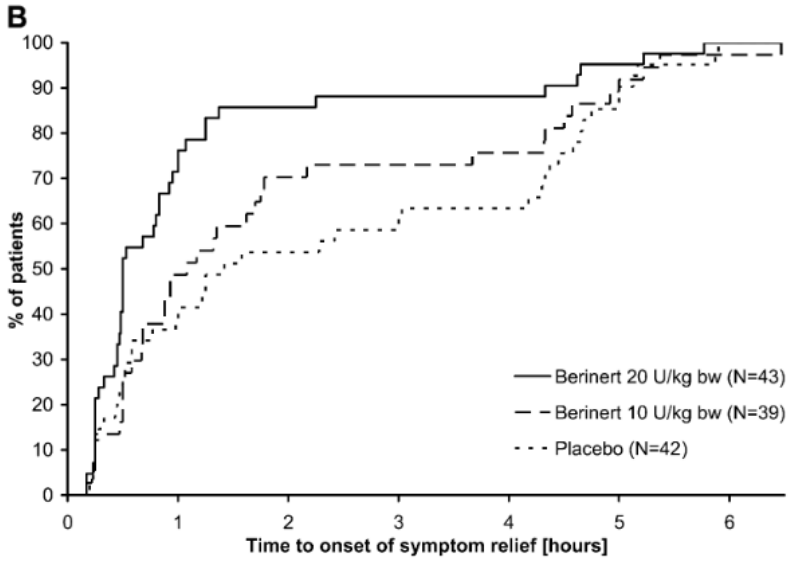
Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks

Timothy J. Craig, MD,[a] Robyn J. Levy, MD,[b] Richard L. Wasserman, PhD, MD,[c] Againdra K. Bewtra, MD,[d] David Hurewitz, MD,[e] Krystyna Obtułowicz, MD,[f] Avner Reshef, MD,[g] Bruce Ritchie, MD,[h] Dumitru Moldovan, MD,[i] Todor Shirov, MD,[j] Vesna Grivcheva-Panovska, MD,[k] Peter C. Kiessling, PhD,[l] Heinz-Otto Keinecke, MS,[m] and Jonathan A. Bernstein, MD[n] *Hershey, Pa, Atlanta, Ga, Dallas, Tex, Omaha, Neb, Tulsa, Okla, Krakow, Poland, Tel Hashomer, Israel, Edmonton, Alberta, Canada, Tirgu Mures, Romania, Sofia, Bulgaria, Skopje, Republic of Macedonia, Marburg, Germany, and Cincinnati, Ohio*

TABLE III. Analyses of time to onset of symptom relief by HAE attack characteristics (intention-to-treat population)

Characteristic	Statistic	Time to onset of symptom relief (h)*		
		Placebo (N = 42)	C1-INH 10 U/kg (N = 39)	C1-INH 20 U/kg (N = 43)
Type of attack†				
Abdominal	N	33	31	34
	Mean (SD)	8.59 (11.083)	7.59 (10.680)	3.37 (7.659)
	Median (range)	1.25 (0.20-24.00)	1.17 (0.17-24.00)	0.50 (0.17-24.00)
Facial	N	8	8	9
	Mean (SD)	15.47 (11.802)	7.02 (10.531)	5.89 (10.274)
	Median (range)	24.00 (0.25-24.00)	1.32 (0.50-24.00)	0.92 (0.25-24.00)
Intensity of attack‡				
Moderate	N	26	32	27
	Mean (SD)	8.92 (11.204)	8.12 (10.885)	4.95 (9.259)
	Median (range)	1.33 (0.25-24.00)	1.13 (0.22-24.00)	0.78 (0.17-24.00)
Severe	N	16	7	16
	Mean (SD)	12.44 (11.953)	4.50 (8.682)	2.11 (5.862)
	Median (range)	13.50 (0.20-24.00)	1.35 (0.17-24.00)	0.50 (0.17-24.00)

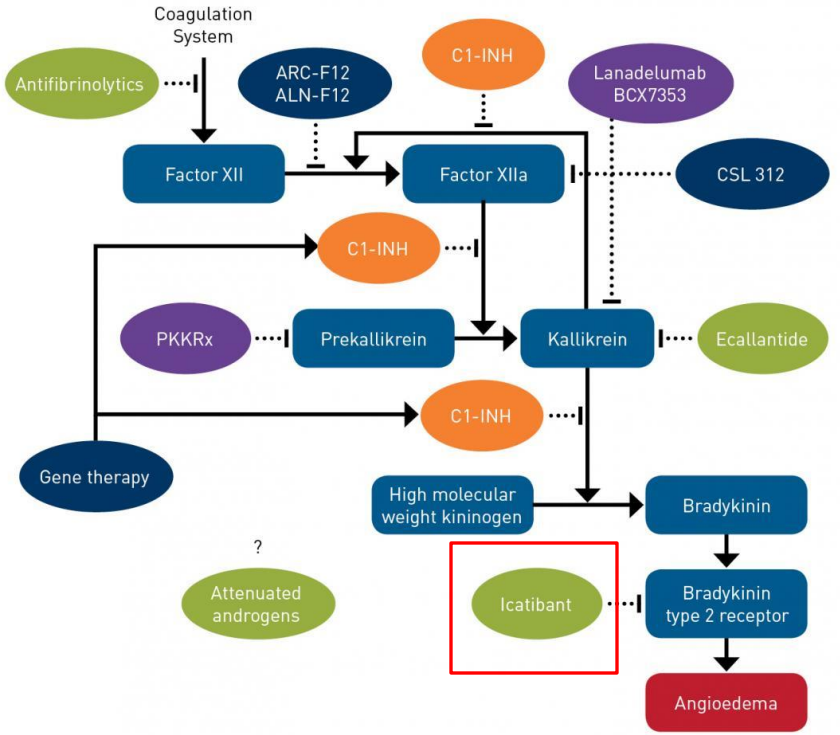
*Time to onset of symptom relief was set to 24 hours if the patient received rescue study medication or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma after 4 hours.
†One patient was originally randomized with a facial attack, which was later reassessed as a laryngeal attack.
‡Assessment of intensity of symptoms of the HAE attack: the intensity (mild, moderate, or severe) was stated by the patient and confirmed by the investigator. Only patients with moderate to severe HAE attacks were to be included in the study.



On-demand treatment

- pdC1-INH replacement 20 U/kg **IV** (Berinert)
- icatibant **subcut** (Firazyr)
  - Covered by Special Authority
  - Pre-filled syringes
  - Patient support program available
  - Nurse will visit patient to provide training

FIGURE 2. Emerging Treatment Options for HAE[2,6,7]



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On-demand treatment

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  - Covered by Special Authority
  - Pre-filled syringes
  - Patient support program available
  - Nurse will visit patient to provide training

Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial

William R. Lumry, MD*; H. Henry Li, MD, PhD†; Robyn J. Levy, MD‡;
Paul C. Potter, FCP(SA), MD (Cape Town)§; Henriette Farkas, MD, PhD, DSc¶;
Dumitru Moldovan, MD, PhD‖; Marc Riedl, MD#; Hongbin Li, MS**; Timothy Craig, DO††;
Bradley J. Bloom, MD**; and Avner Reshef, MD‡‡

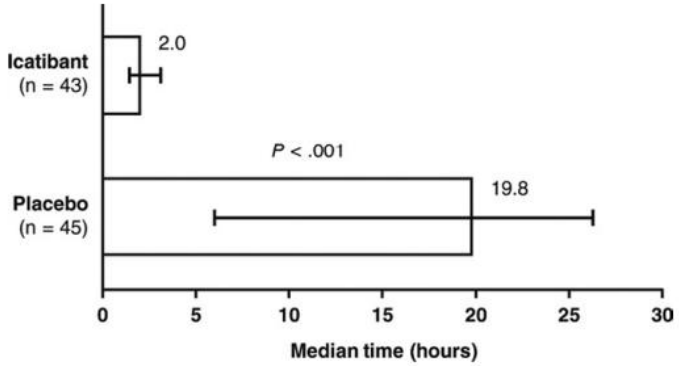

Figure 2. Median (95% CI) time to onset of symptom relief (*nonlaryngeal ITT population*). Subjects who did not achieve symptom relief within the observation period were censored at the last observation time (icatibant, $n = 0$; placebo, $n = 3$).

Table 2. Time to Symptom Improvement for Cutaneous and Abdominal Attacks (*Nonlaryngeal ITT Population*)

	Icatibant ($n = 43$)	Placebo ($n = 45$)	Peto-Peto Wilcoxon P
Time to onset of symptom relief,[a] hours	2.0 (1.5, 3.0)	19.8 (6.1, 26.3)	<.001
Time to onset of primary symptom relief,[b] hours	1.5 (1.0, 2.0)	18.5 (3.6, 23.9)	<.001
Time to subject-assessed initial symptom relief,[c] hours	0.8 (0.5, 1.0)	3.5 (1.9, 5.4)	<.001
Time to investigator-assessed initial symptom relief,[c] hours	0.8 (0.6, 1.3)	3.4 (2.6, 6.0)	<.001
Time to almost complete symptom relief,[d] hours	8.0 (5.0, 42.5)	36.0 (29.0, 50.9)	.012
Time to onset of symptom relief for subject-assessed composite Symptom Score,[e] hours	2.0 (1.5, 2.0)	8.0 (4.0, 23.9)	<.001
Time to onset of symptom relief for investigator-assessed composite Symptom Score,[e] hours	1.6 (1.0, 2.5)	– (3.5, —)	<.001
Time (hours) to onset of symptom relief for individual symptom VAS score,[f] hours			
Skin swelling	3.0	22.3	<.001
Skin pain	2.0	8.0	.013
Abdominal pain	1.8	3.5	.007

On-demand treatment

Special populations?

Pregnancy

- C1-INH 20 U/kg IV
- “Icatibant … may be used in the case of life-threatening attacks during pregnancy when pdC1-INH is not available or has not been efficacious”

Acute treatment and short-term prophylaxis of HAE in pregnant patients

13. pdC1-INH is the treatment of choice for angioedema attacks in pregnant HAE-1/2 patients Consensus, Strong

Management Approach

1. Trigger avoidance
2. On-demand therapy
3. **Short-term prophylaxis**
4. Long-term prophylaxis
5. Genetic counselling

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Short-term prophylaxis

Use of medication **prior** to known triggers to reduce risk

- Physical trauma, e.g. medical, dental procedures
- Recommended:
  - C1-INH 20 U/kg IV, within 1 hour of procedure

Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study

Konrad Bork, MD,[a] Jochen Hardt, PhD,[b] Petra Staubach-Renz, MD,[a] and Guenther Witzke, PhD,[a] Mainz, Germany
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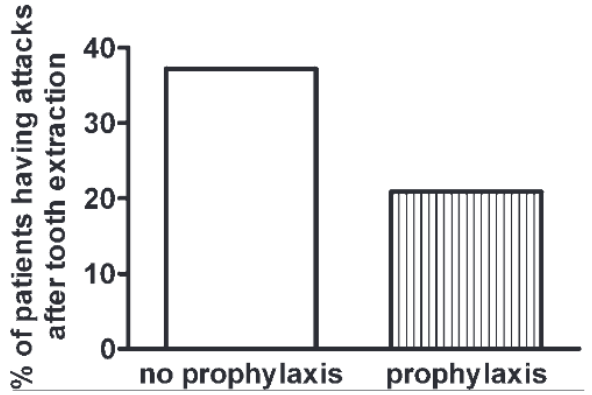

Fig. 1. Percentage of patients with hereditary angioedema who developed attacks following tooth extraction with and without short-term prophylaxis with C1 inhibitor concentrate. Note that some patients received prophylaxis with 500 U or 1,000 U C1 inhibitor concentrate for different tooth extractions. No significance test was performed.

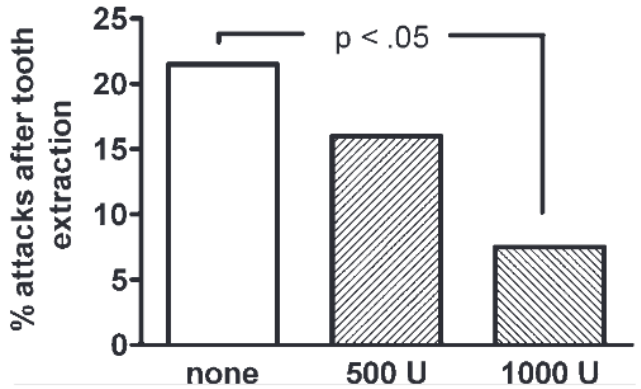

Fig. 2. Percentage of tooth extractions followed by attacks, without prophylaxis and with short-term prophylaxis with 500 U and 1,000 U C1 inhibitor concentrate.

Management Approach

1. Trigger avoidance
2. On-demand therapy
3. Short-term prophylaxis
4. **Long-term prophylaxis**
5. Genetic counselling

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Long-term Prophylaxis

Regular use of medication to reduce or prevent attacks

Initiation based on shared decision making with the patient

- More strongly recommended for frequent attacks
- Or severe attacks, such as laryngeal and abdominal attacks

Approach to individualized therapy

37. The decision to start or stop long-term prophylaxis depends on multiple factors and should be made by the patient and an HAE specialist	Consensus, Strong

Long-term Prophylaxis

- Options:
  - First-line
    - C1-INH
      - IV
      - **Subcut**
    - Icatibant
    - Lanadelumab
    - Berotralstat
  - Not first-line
    - Attenuated androgens (e.g. Danazol)
    - Anti-fibrinolytics (e.g. TXA)

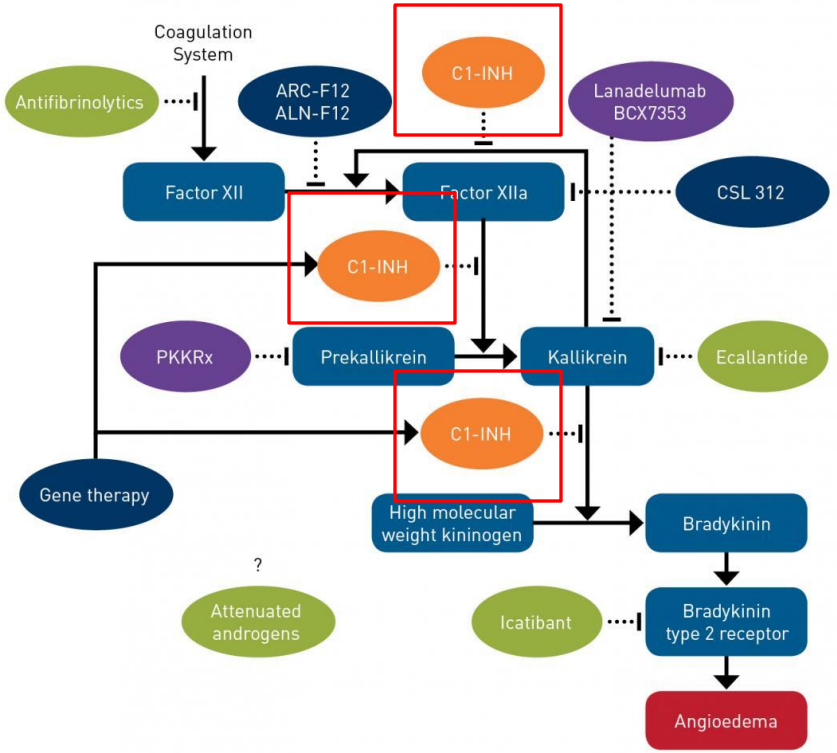
Long-term prophylaxis in HAE-1 and HAE-2

25. Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration, and severity of attacks	High, Strong
26. pdC1-INH is an effective therapy for long-term prophylaxis in patients with HAE-1/2	High, Strong
27. Lanadelumab is an effective therapy for long-term prophylaxis in patients with HAE-1/2	High, Strong
28. Subcutaneous C1-INH or lanadelumab should be used as first-line therapy for long-term prophylaxis in patients with HAE-1/2	Consensus, Strong

Long-term Prophylaxis

- C1-INH
  - IV
  - Subcut
- Lanadelumab
- Berotralstat

FIGURE 2. Emerging Treatment Options for HAE[2,6,7]



C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

Long-term Prophylaxis

C1 INH – regular “top-up” of C1 INH

- IV – Cinryze (on-label) 1000 U q3-4days
- IV – Berinert (off-label) 20 U/kg q3-4days

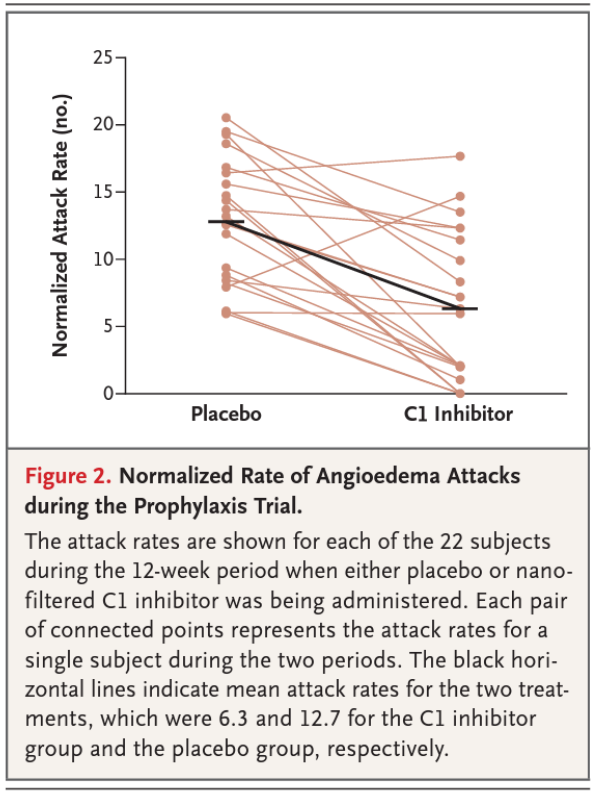


Figure 2. Normalized Rate of Angioedema Attacks during the Prophylaxis Trial.

The attack rates are shown for each of the 22 subjects during the 12-week period when either placebo or nanofiltered C1 inhibitor was being administered. Each pair of connected points represents the attack rates for a single subject during the two periods. The black horizontal lines indicate mean attack rates for the two treatments, which were 6.3 and 12.7 for the C1 inhibitor group and the placebo group, respectively.

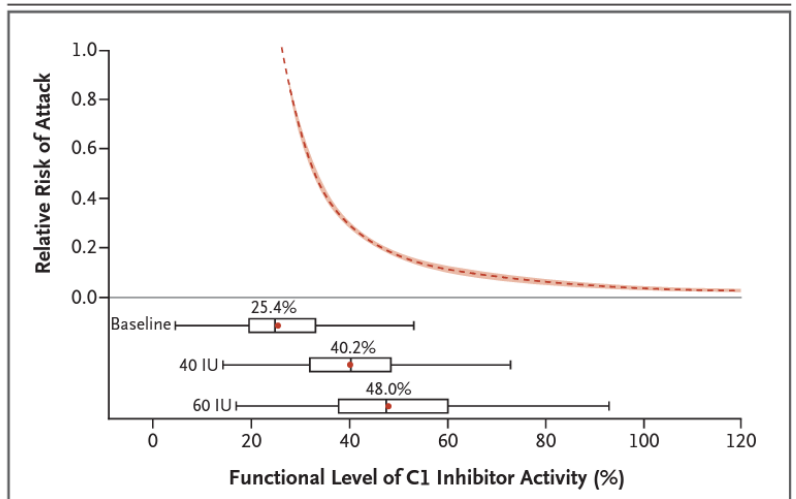


Figure 2. Relationship between Functional Levels of C1 Inhibitor Activity and the Relative Risk of an Attack of Hereditary Angioedema.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 5, 2010 VOL. 363 NO. 6

Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema

Long-term Prophylaxis

C1 INH – regular “top-up” of C1 INH

- Subcut – Haegarda 60 U/kg subcut q3-4days

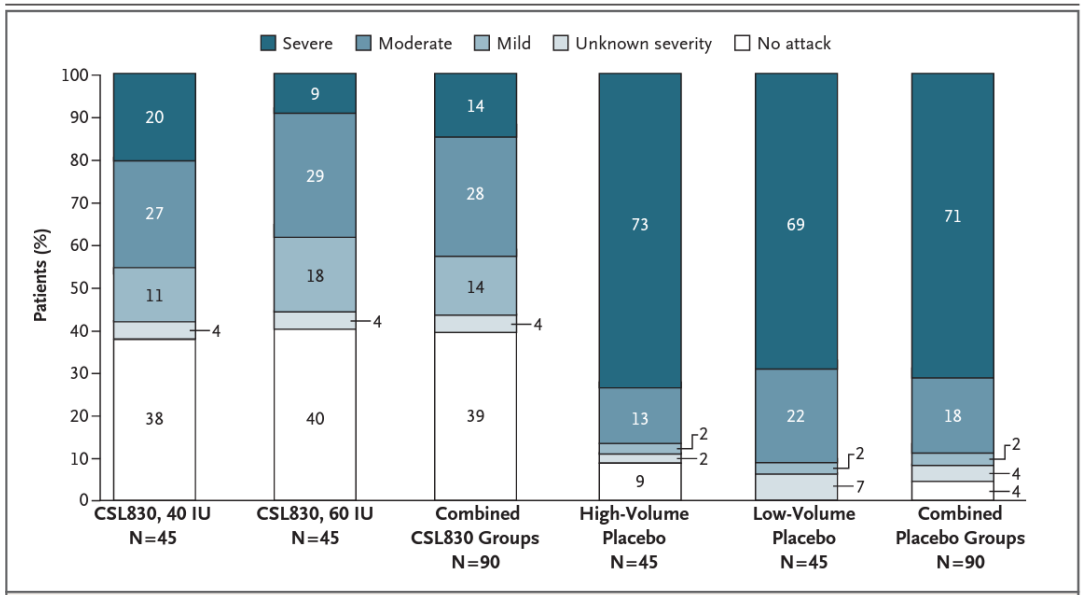


Figure 1. Attacks of Hereditary Angioedema, According to the Maximum Severity of the Attack.

The investigator graded the severity of each attack according to the intensity of the most severe symptom among the patients in the intention-to-treat population. Percentages may not total 100 because of rounding.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

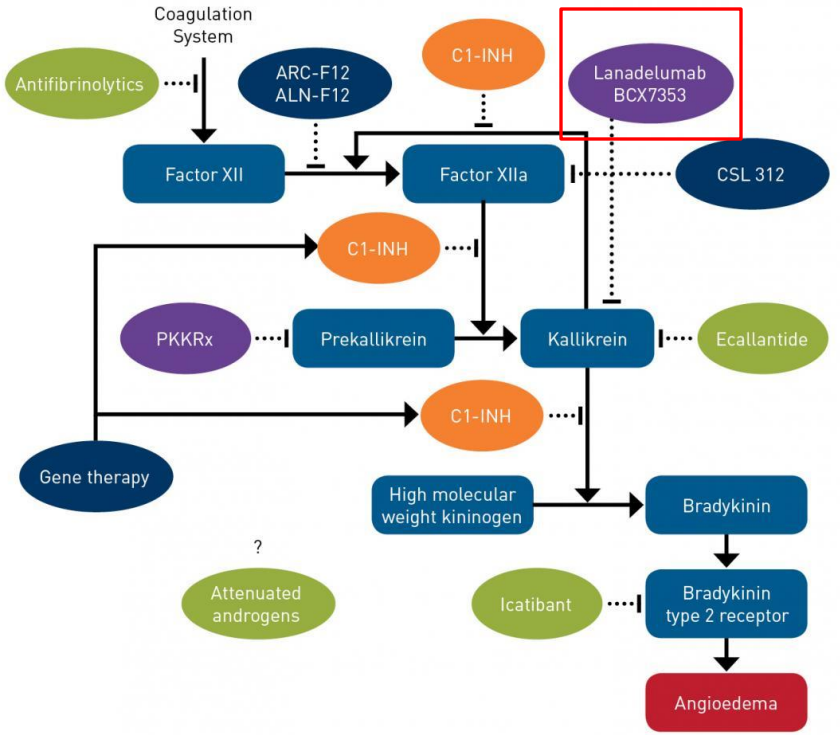
Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor

H. Longhurst, M. Cicardi, T. Craig, K. Bork, C. Grattan, J. Baker, H.H. Li, A. Reshef, J. Bonner, J.A. Bernstein, J. Anderson, W.R. Lumry, H. Farkas, C.H. Katelaris, G.L. Sussman, J. Jacobs, M. Riedl, M.E. Manning, J. Hebert, P.K. Keith, S. Kivity, S. Neri, D.S. Levy, M.L. Baeza, R. Nathan, L.B. Schwartz, T. Caballero, W. Yang, I. Crisan, M.D. Hernandez, I. Hussain, M. Tarzi, B. Ritchie, P. Králíčková, M. Guilarte, S.M. Rehman, A. Banerji, R.G. Gower, D. Bensen-Kennedy, J. Edelman, H. Feuersenger, J.-P. Lawo, T. Machnig, D. Pawaskar, I. Pragst, and B.L. Zuraw, for the COMPACT Investigators*

Long-term Prophylaxis

- C1-INH
  - IV
  - Subcut
- Lanadelumab
- Berotralstat

FIGURE 2. Emerging Treatment Options for HAE[2,6,7]



C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

Long-term Prophylaxis

Lanadelumab (Takhzyro) – approved in 2018

- Humanized antibody inhibiting kallikrein
- Dose – age 12 and above
  - 300mg subcut q2weeks
  - Can consider q4weeks if well-controlled over 6 months
- Cost?
  - $20,538 per vial/prefilled syringe

JAMA | Original Investigation

Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks
A Randomized Clinical Trial

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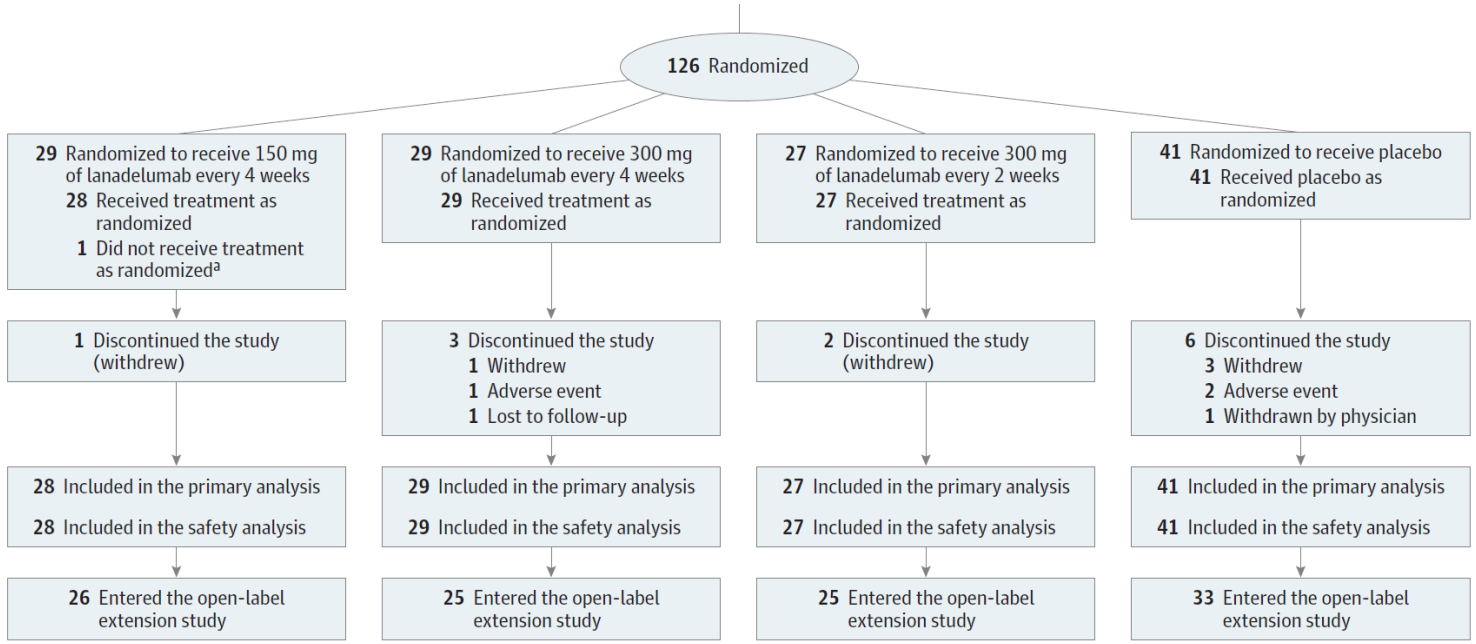

All patients received injections every 2 weeks, with those in the every-4-week groups receiving placebo in between active treatments.

[a] One patient was determined to be a screen failure after randomization to the group that received 150 mg of lanadelumab every 4 weeks. This patient was not treated and was withdrawn from the study. This patient was counted in the randomized population but was excluded from both the intent-to-treat and safety populations.

Long-term Prophylaxis

Lanadelumab (Takhzyro)

- Humanized antibody inhibiting kallikrein
- Dose – age 12 and above
  - 300mg subcut q2weeks
  - Can consider q4weeks if well-controlled over 6 months
- Cost?
  - $20,538 per vial/prefilled syringe

JAMA | Original Investigation

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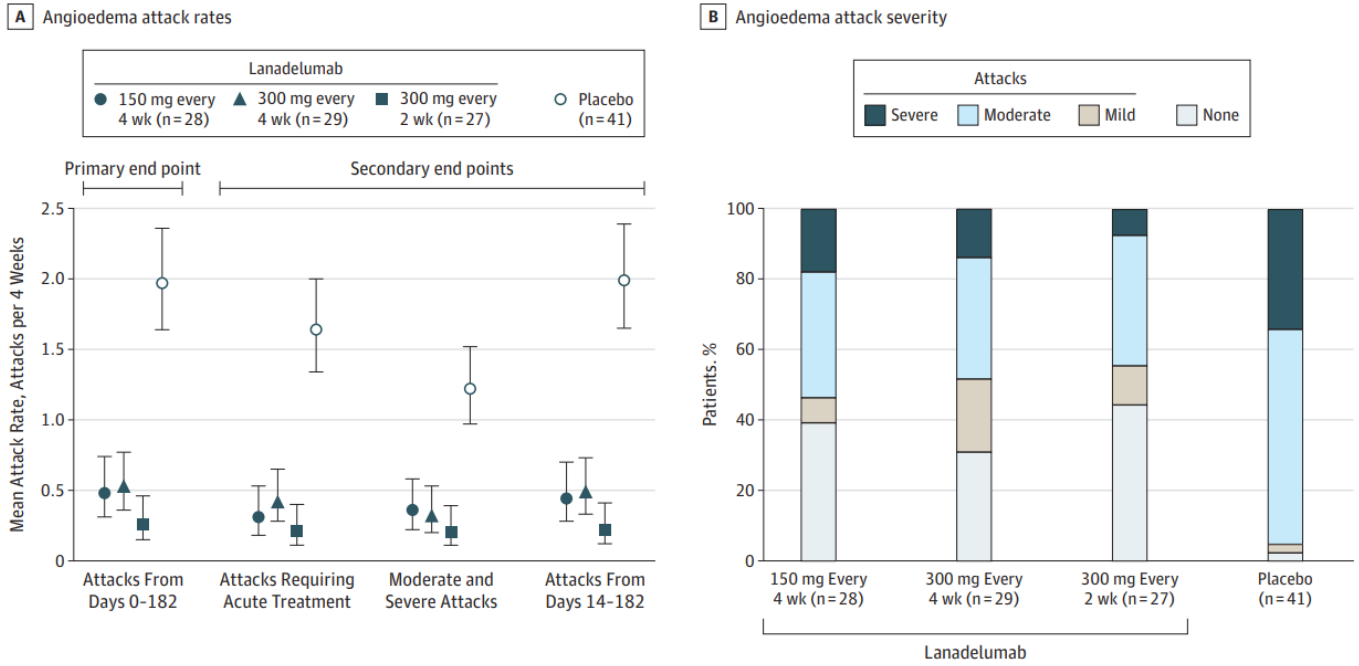
Figure 2. Primary and Secondary Efficacy End Points and Maximum Severity of Investigator-Confirmed Hereditary Angioedema Attacks From Days 0-182



All patients received injections every 2 weeks, with those in the every-4-week groups receiving placebo in between active treatments.

A, Attack rates are model-based mean attacks per month, with a month defined as 4 weeks. The mean attack rate for each group is presented with error bars representing 95% CI.

B, Maximum hereditary angioedema attack severity is the most severe attack reported by the patient. For patients who did not complete the study, all available data were used for classification.

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Table 5. Adverse Events[a]

	No. (%) of Patients				
	Lanadelumab				
	Every 4 Weeks		300 mg		
Adverse Events[b]	150 mg (n = 28)	300 mg (n = 29)	Every 2 Weeks (n = 27)	Total (n = 84)	Placebo (n = 41)
Any adverse event	25 (89.3)	25 (86.2)	26 (96.3)	76 (90.5)	31 (75.6)
Injection site pain	13 (46.4)	9 (31.0)	14 (51.9)	36 (42.9)	12 (29.3)
Viral upper respiratory tract infection	3 (10.7)	7 (24.1)	10 (37.0)	20 (23.8)	11 (26.8)
Headache	3 (10.7)	5 (17.2)	9 (33.3)	17 (20.2)	8 (19.5)
Injection site					
Erythema	4 (14.3)	2 (6.9)	2 (7.4)	8 (9.5)	1 (2.4)
Bruising	3 (10.7)	2 (6.9)	1 (3.7)	6 (7.1)	0
Dizziness	1 (3.6)	3 (10.3)	1 (3.7)	5 (6.0)	0
Any treatment-related adverse event[c]	17 (60.7)	14 (48.3)	19 (70.4)	50 (59.5)	14 (34.1)
Injection site					

Long-term Prophylaxis

Lanadelumab (Takhzyro)

- Cost?
  - $20,538 per vial/prefilled syringe

Coverage Criteria

Initiation criteria

1. The patient is at least 12 years of age.
2. The diagnosis of HAE type I or II is made by a specialist physician who has experience in the diagnosis of HAE.
3. The patient has experienced at least three HAE attacks within any four-week period before initiating lanadelumab therapy that required the use of an acute injectable treatment.

Renewal criteria

1. An assessment of a response to treatment should be conducted six months after initiating treatment with lanadelumab.
2. A response to treatment is defined as a 50% or greater reduction in the number of HAE attacks for which acute injectable treatment was received within the initial six months of treatment with lanadelumab compared to the rate of attacks observed before initiating treatment with lanadelumab.
3. Following the initial six-month assessment, patients should be assessed for continued response to lanadelumab every twelve months.
4. Continued response is defined as no increase in the number of HAE attacks for which acute injectable treatment was received compared with the number of attacks observed prior to initiating treatment with lanadelumab.

Discontinuation criteria

1. Treatment with lanadelumab should be discontinued in patients who either respond inadequately or exhibit a loss of response, defined as follows:
   a. Inadequate response: No reduction in the number of HAE attacks for which acute injectable treatment was received during the first six months of treatment with lanadelumab.
   b. Loss of response: An increase in the observed number of HAE attacks for which acute injectable treatment was received before initiating treatment with lanadelumab.

BRITISH COLUMBIA Ministry of Health

Lanadelumab (Takhzyro®)
Hereditary Angioedema
B.C Expensive Drugs for Rare Diseases Renewal Form (Rev 2023/7/4)

Ministry/PHSA Use Only

EDRD Case No: | **Submission Date:**

I. Patient Information

PHN:

II. Prescriber Information

Name: Dr.

I am a specialist who is experienced in the diagnosis and management of patients with angioedema.
☐ Yes ☐ No

Email:

MOA: | **MOA Email:** | **MOA Phone:**

III. Drug and Drug Coverage Information

Dosing:
a) **300mg q 2 weeks** ☐ b) **300mg q 3 weeks** ☐ c) **300mg q 4 weeks** ☐
b) **For alternate dosing, please indicate the dose and reason:**

Approval period: 12 months

Dosage Form: injectable solution single vial form

Price: $20,538 per vial/pre-filled syringe

I certify that:

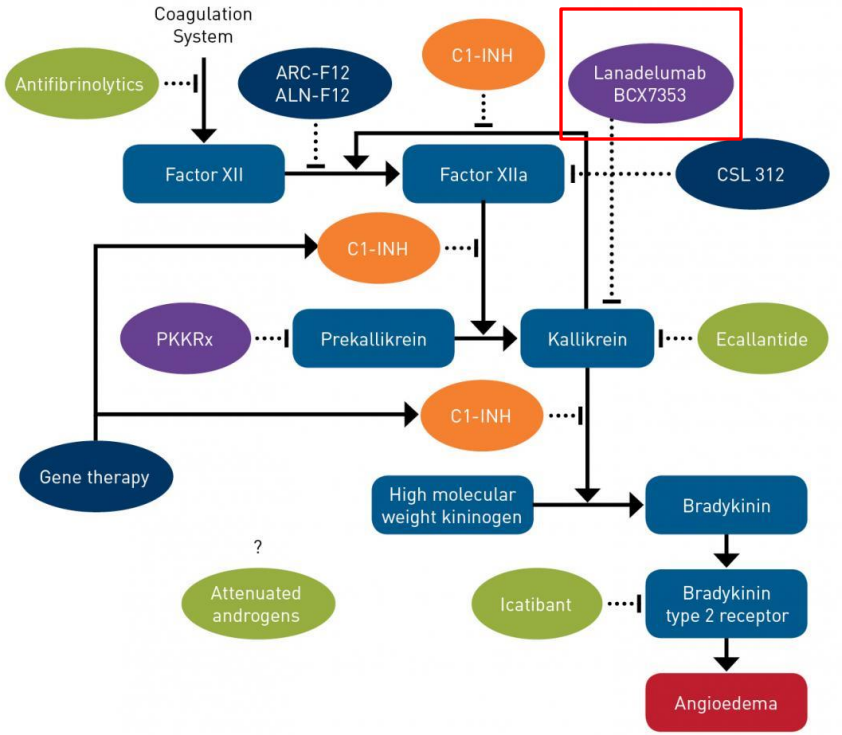
☐ Lanadelumab will not be used in combination with other medications used for long-term prophylactic treatment of angioedema (e.g., C1-INH). However, short-term concurrent use is permitted to provide adequate prophylactic coverage while lanadelumab reaches steady state levels in the patient.

☐ The dose of lanadelumab will not be escalated to more than 300mg every two weeks in cases of inadequate response or loss of response.

Long-term Prophylaxis

- C1-INH
  - IV
  - Subcut
- Lanadelumab
- Berotralstat

FIGURE 2. Emerging Treatment Options for HAE[2,6,7]



C1-INH indicates component 1 esterase inhibitor; HAE, hereditary angioedema.

Long-term Prophylaxis

Berotralstat (Orladeyo) – approved in 2022

- Oral kallikrein inhibitor
- Dose – 12 or older in US/Canada, 18 or older in Europe
  - 110mg or 150mg po daily

End point	110 mg (n = 41)	150 mg (n = 40)	Placebo (n = 40)
Primary			
Estimated monthly investigator-confirmed attack rate through week 24*	1.65	1.31	2.35
Attack rate ratio relative to placebo (95% CI)	0.70 (0.51-0.95)	0.56 (0.41-0.77)	—
P value	.024	<.001	—
Secondary			
CFB to week 24 in AE-QoL total score, LSM (SE)†	–12.46 (2.53)	–14.59 (2.59)	–9.69 (2.64)
Difference from placebo, LSM (95% CI)	–2.77 (–10.08 to 4.53)	–4.90 (–12.23 to 2.43)	—
P value	.453	.188	—
Proportion of days with angioedema symptoms, LSM (SE)‡	0.134 (0.019)	0.119 (0.019)	0.197 (0.020)
Difference from placebo, LSM (95% CI)	–0.062 (–0.117 to –0.008)	–0.078 (–0.133 to –0.023)	—
Nominal *P* value	.025	.006	—
Estimated monthly confirmed attack rate over the effective dosing period (day 8 to week 24)*§	1.65	1.27	2.38
Attack rate ratio relative to placebo (95% CI)	0.70 (0.51-0.96)	0.54 (0.39-0.74)	—
Nominal *P* value	.026	<.001	—

Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial

Check for updates

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San Diego, Los Angeles, and Walnut Creek, Calif; Dallas, Tex; Charlotte and Durham, NC; Frankfurt and Berlin, Germany; Boston, Mass; Cincinnati, Ohio; Little Rock, Ark; Spokane, Wash; Québec City, Québec, and Ottawa, Ontario, Canada; St Louis, Mo; Vienna, Austria; Brno and Plzen, Czech Republic; Birmingham, Ala; Columbus, Ohio; Portland, Ore; New York, NY; Hershey, Pa; Chevy Chase, Md; Budapest, Hungary; and Berlin, Germany

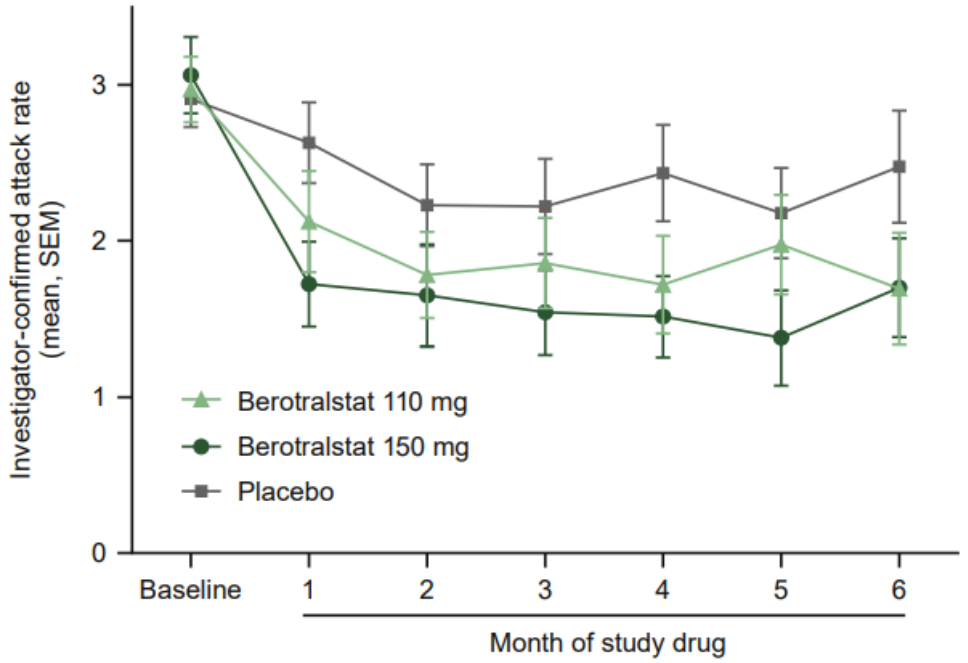

FIG 1. Mean investigator-confirmed attack rate by month in the intent-to-treat population.

Long-term Prophylaxis

Berotralstat (BCX7353) – approved in 2022

- Oral kallikrein inhibitor
- Dose – 12 or older in US/Canada, 18 or older in Europe
  - 110mg or 150mg po daily

Anaphylaxis, drug allergy, urticaria, and angioedema

Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial

Check for updates

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TABLE III. Summary of TEAEs, safety population

TEAE, no. (%)	Berotralstat 110 mg (n = 41)	Berotralstat 150 mg (n = 40)	Placebo (n = 39)
Any TEAE	34 (83)	34 (85)	30 (77)
Any TESAE	1 (2)	0	3 (8)
Any drug-related TESAE	0	0	0
Any grade 3 or 4 TEAE*	5 (12)	1 (3)	4 (10)
TEAEs leading to discontinuation	3 (7)	1 (3)	1 (3)
TEAE (EOSI), investigator-identified rash	0	1 (3)	0
Drug-related investigator-identified rash	0	0	0
Most frequent TEAEs (≥10% in any treatment arm)			
Upper respiratory tract infection	13 (32)	12 (30)	11 (28)
Nausea	6 (15)	6 (15)	7 (18)
Abdominal pain	4 (10)	9 (23)	4 (10)
Vomiting	4 (10)	6 (15)	1 (3)
Diarrhea	4 (10)	6 (15)	0
Headache	3 (7)	4 (10)	2 (5)
Back pain	1 (2)	4 (10)	1 (3)

EOSI, Event of special interest

Case 3

Treatment

- Trigger avoidance
  - No medications of concern, no procedures planned
- Provided access to icatibant 30mg subcut q8h PRN (at least 2 doses) immediately
  - OnePath Patient Support Program is a great resource!
- Discussed long-term prophylaxis
  - Patient interested in pursuing
  - C1-INH subcut replacement, lanadelumab and berotralstat discussed
  - Lanadelumab application pursued, started in March 2023
- AECT
  - Feb 2023 – 1
  - Sept 2023 – 15
- Genetic counselling
  - Son in Canada tested and had normal C4 and C1-INH

Acquired Angioedema

Pathophysiology

- **Overconsumption of C1-INH**
- Overactivation of classical complement pathway (previously type I)
  - Immune-complex complement activation
- Autoantibodies against C1-INH (previously type II)
  - C1-INH cleaved without inactivation of target

Epidemiology

- Prevalence: 1 in 500,000
- Age of onset: >40 years in 94% of patients

Zingale, L. C., Castelli, R., Zanichelli, A., & Cicardi, M. (2006). Acquired Deficiency of the Inhibitor of the First Complement Component: Presentation, Diagnosis, Course, and Conventional Management. Immunology and Allergy Clinics of North America. https://doi.org/10.1016/j.iac.2006.08.002

Acquired angioedema

Associated conditions (found in 70% of patients):

- Angioedema may precede other conditions by years
- B-cell lymphoproliferative disorders
  - Non-hodgekin's lymphoma
- MGUS
- Multiple myeloma
- Waldenstrom macroglobulinemia
- Autoimmune disorders
  - SLE
  - eGPA
- Infections
  - HIV, HBV

TABLE I. Characteristics of patients with C1-INH-AAE (N =77)

Characteristic	
Age (y), median (IQR)	70 (64-78)
Sex, n (%)	
Males	32 (42)
Females	45 (58)
Age at symptom onset (y), median (IQR)	62 (51.0-68)
Age at diagnosis (y), median (IQR)	64 (55-72)
Delay in diagnosis (y), median (IQR)	2 (1-5)
Follow-up period (y), median (IQR)	8 (2-15)
Complement parameters,* n (%)	
C1-INH antigen	25 (9-27)
C1-INH activity	13 (4-25)
C4	9 (4-25)
C1q	21 (6-25)
Patients tested for autoantibodies to C1-INH, n (%)	73 (95)
Positive for autoantibodies to C1-INH, n (%)	48 (68)
Patients with lymphoproliferative disease (excluding MGUS), n (%)	24 (31)
Positive for autoantibodies to C1-INH, n (%)	14 (58)
Patients with MGUS, n (%)	32 (42)
Positive for autoantibodies, n (%)	22 (69)

IQR, Interquartile range; *MGUS*, monoclonal gammopathy of undetermined significance; *N*, total number of patients; *n*, number of patients with data.
*Values indicate activity relative to normal human plasma.

Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema

M. CICARDI, A. BERETTA, M. COLOMBO, D. GIOFFRÉ, M. CUGNO & A. AGOSTONI *Institute of Internal Medicine, University of Milan and IRCCS Maggiore Hospital of Milan, Milan, Italy*

Otani, I. M., & Banerji, A. (2017). Acquired C1 Inhibitor Deficiency. Immunology and Allergy Clinics of North America, 37(3), 497–511. https://doi.org/10.1016/j.iac.2017.03.002
Zanichelli, A., Azin, G. M., Wu, M. A., Suffritti, C., Maggioni, L., Caccia, S., Perego, F., Vacchini, R., & Cicardi, M. (2017). Diagnosis, Course, and Management of Angioedema in Patients With Acquired C1-Inhibitor Deficiency. The Journal of Allergy and Clinical Immunology: In Practice, 5(5), 1307–1313.
https://doi.org/10.1016/j.jaip.2016.12.032

Acquired angioedema

Symptoms:

- Difficult to differentiate from hereditary angioedema
- Angioedema:
  - Typically gradual worsening over 1.5d, then lasting 3-5d
  - Cutaneous, laryngeal and abdominal attacks

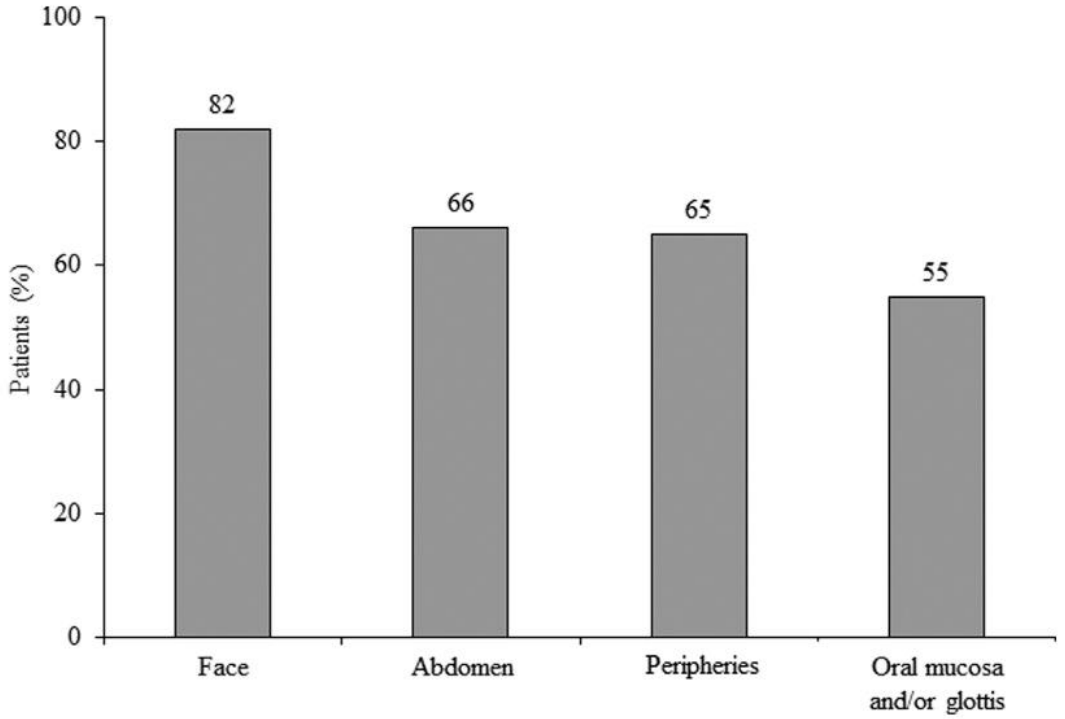

FIGURE 1. Locations of angioedema attacks in patients with C1-INH-AAE (N = 77). N, Total number of patients.

Otani, I. M., & Banerji, A. (2017). Acquired C1 Inhibitor Deficiency. Immunology and Allergy Clinics of North America, 37(3), 497–511. https://doi.org/10.1016/j.iac.2017.03.002

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Acquired angioedema

Investigations

- C4
- C1INH level and function
- C1q and anti-C1-INH

Table 1
Complement level patterns for hereditary and acquired C1 esterase inhibitor deficiencies

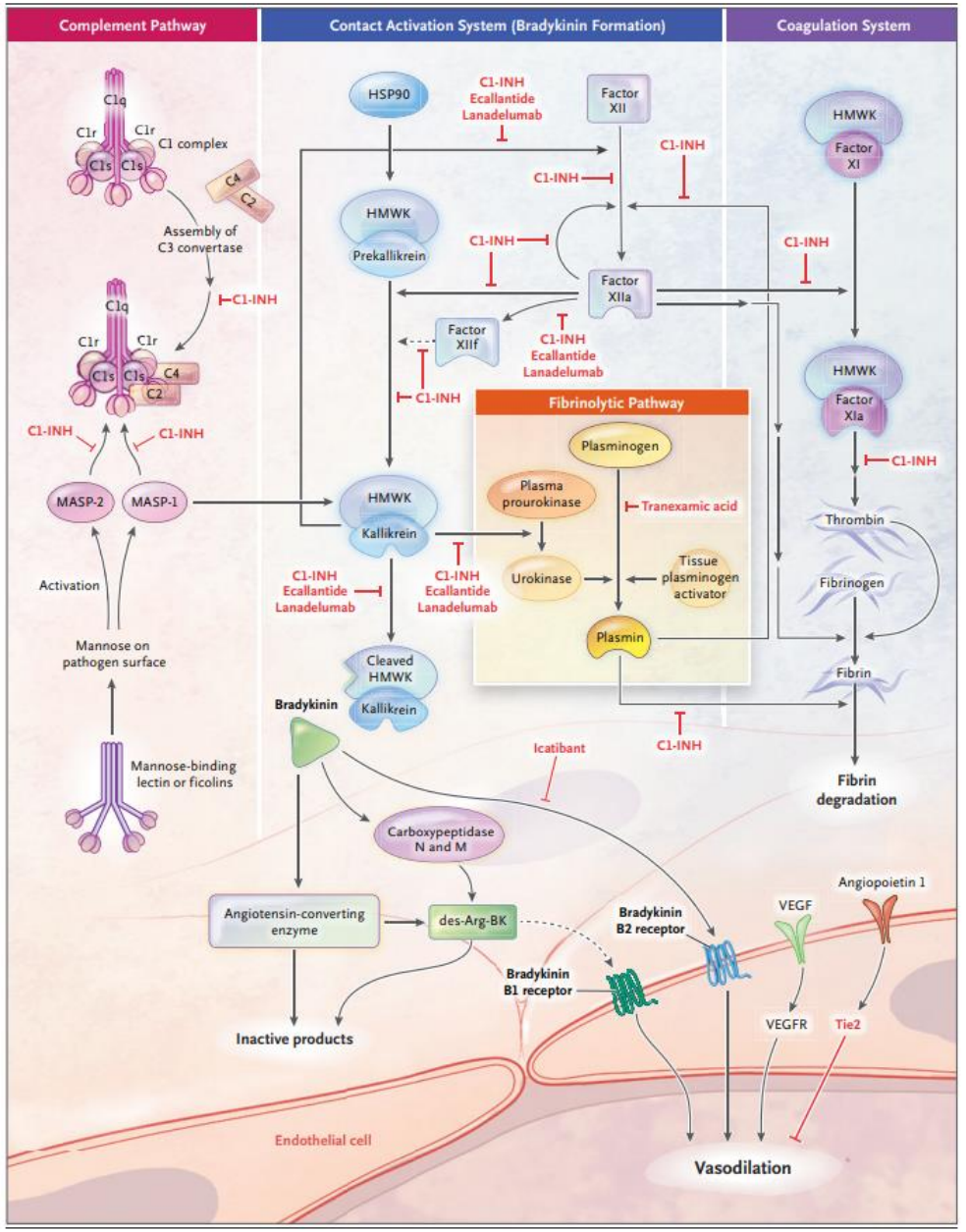
Diagnosis	C1-INH	C1-INH Function	C4	C1q	Anti-C1-INH
HAE with C1-INH deficiency	Low	Low	Low	Normal	Absent
HAE type II	Normal	Low	Low	Normal	Absent
AAE type I	Low	Low	Low	Low	Absent
AAE type II	Low/normal	Low	Low	Low	Present

Otani, I. M., & Banerji, A. (2017). Acquired C1 Inhibitor Deficiency. Immunology and Allergy Clinics of North America, 37(3), 497–511. https://doi.org/10.1016/j.iac.2017.03.002

Acquired angioedema

Investigations

- C4
- C1INH level and function
- C1q and anti-C1-INH



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Acquired Angioedema

Treatment

- Address underlying cause
  - Rituximab
- Usual HAE management

Table II Rituximab and combined treatments, and their clinical and biological efficacies

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Treatment regimen							
Rituximab cycle[a] (n infusions)	2 (8)	2 (8)	1 (4) + 1 g	1 (4)	1 (4)	1 (4) + 1 g (2) 1 y + 1 g (2) 2 yr	1 (4) + 1 (4) 2 yr later
Combined agent(s)	CS, TA	CYC (IV 1.5 g)	CS	None	Danazol	None	None
C1INH antigen (N 210–345), mg/l							
Initial	139	96	170	144	80	16	81
After 1st cycle	134	147	192	14	87	123	98
After 2nd cycle	195	230	NA	NA	NA	126	154
4–6 mo later	227	202	104	155	89	92	ND
C1INH function (N 17.2–27.4), U/ml							
Initial	5	5.4	2.7	4.9	ND	<2	ND
After 1st cycle	8.1	8.2	ND	2.9	2	<2	7.6
After 2nd cycle	14.1	16.1	ND	NA	NA	<2	10
4–6 mo later	16.1	13.3	ND	4.1	3.7	<2	ND
Anti-C1INH autoantibody isotype/titer (N <100), U							
Initial	IgM/2320	IgM/271	IgA/339	IgG/1000	IgM/317	IgM/positive	Undetectable
After 1st cycle	2000	432	ND	1170	620	Positive	Undetectable
After 2nd cycle	1290	358	ND	NA	NA	Positive	Undetectable
4–6 mo later	760	378	ND	1170	697	Positive	Undetectable
After rituximab							
Clinical outcome	1 attack	No subsequent attack	2 labial AAE attacks	No subsequent attack	Less severe AAE	AAE worsening	Attacks every 15 d
Continued treatment (s)							
Prophylaxis	TA	ND	Prednisone	None	Danazol, TA	None	TA
For attacks	TA, C1INH concentrate	C1INH concentrate	C1INH concentrate	TA, C1INH concentrate			TA

Branellec, A., Bouillet, L., Javaud, N., Mekinian, A., Boccon-Gibod, I., Blanchard-Delaunay, C., ... Fain, O. (2012). Acquired C1-inhibitor deficiency: 7 patients treated with rituximab. Journal of Clinical Immunology. https://doi.org/10.1007/s10875-012-9691-2

Objectives

Review clinical features of urticaria and angioedema that differentiate them from other presentations

Develop an approach to diagnosis of urticaria and angioedema

Understand guideline level recommendations for treatment options in urticaria and angioedema

Questions?