

ANGIOEDEMA

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59 year old female patient

- Moderate anxiety disorder
- No other medical history
- **TTT** : venlafaxine 1x/d

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59 year old female patient

April 2024:

- Angioedema (right cheek and right upper lip, lower lip) upon waking on 23.04
- Possible ingestion of almonds the day before
- No severity criteria, no urticaria
- In the Emergency Department, resolved the same day with Tavegyl + IV Solumedrol
- Exposure to almonds afterwards, without any adverse reaction

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February 2025:

- Diffuse facial angioedema (right > left) in the morning
- No urticaria
- Context: consumption of chocolate cake (possible nuts) + wine the day before. No associated medication

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February 2025:

- HUG Emergency Department : good initial response to Tavegyl + Solumedrol, but recurrence the next day requiring re-administration
- Favorable course over 48–72 hours
- Re-exposure to chocolate, chocolate cake and various tree nuts without adverse reaction
- No family history of angioedema

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- Tree nut allergy + co factor (wine consumption) + rebound effect?



- Bradykinin mediated?

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Workup

20.06.2025 05.08.2025 05.08.2025 07.08.2025

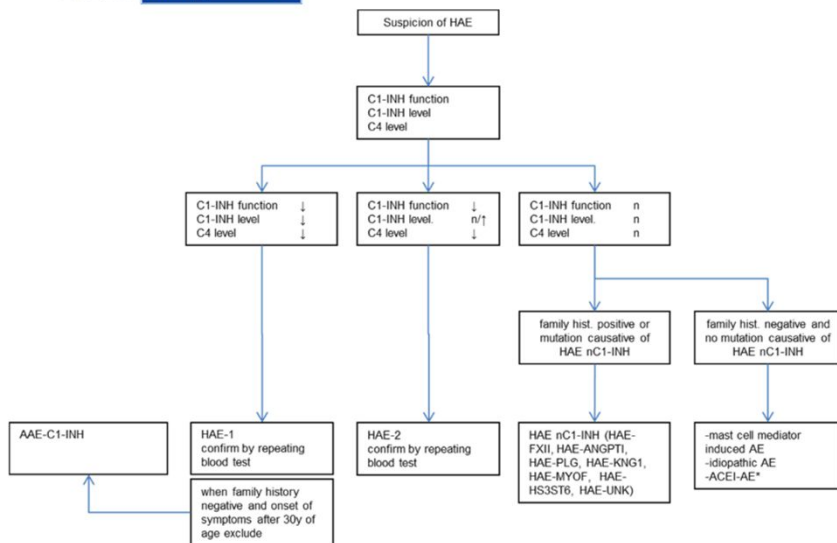
S-complément C4	g/l	0.08 - 0.34	<0.02 [g]			
P-C1 inhibiteur fonctionnel	%	> 68	[M]		6	
S-C1 estérase inhibiteur pondéral	g/l	0.21 - 0.39	<0.03 [g]		<0.03	

Normal C1q

Monoclonal IgM kappa

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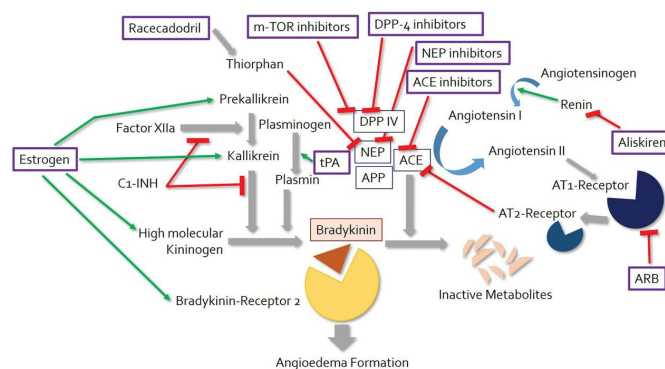
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Initial management

- Hematology referral
- Strong recommendation to visit the ER quickly in the event of a new swelling (as conventional treatment with Anti-H1 and corticosteroids could be ineffective)
- “Allergy” passport : Avoidance of drugs leading to accumulation of bradykinin (e.g. ACE inhibitors, DPP-4 inhibitors, etc.)

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Concomitant medication in patients with bradykinin-mediated angioedema – there's more than ACE inhibitors



ACE, Angiotensin Converting Enzyme; APP, Aminopeptidase P; ARB, Angiotensin II receptor blocker; AT, Angiotensin; C1-INH, C1 inhibitor; DPP-4, Dipeptidyl peptidase-4; mTOR, mechanistic target of rapamycin; NEP, Neprilysin; tPA, Tissue plasminogen activator

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- **05.08.2025 :**

- 3rd recurrence of facial angioedema (cheeks, lips), without dyspnea / dysphagia / dysphonia, no tongue swelling and no skin lesions
- Prednisone 100 mg + 2 Cetallerg tablets in the morning, almost no effect
- HUG Emergency Department, initial treatment: Solumedrol 125 mg + Tavegyl 2 mg IV
- ENT evaluation: No laryngeal edema
- After 1 hour: no improvement → administration of Cinryze 1000 IU IV
- Persistence of swelling → second administration of Cinryze 1000 IU IV

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Hematology workup

- **Flow Cytometry (peripheral blood):**
Monoclonal kappa B-lymphocyte population, CD5- CD10-, representing 61% of circulating lymphocytes
- **Bone marrow aspirate/biopsy — histology:**
Paratrabecular infiltration, representing 20% of total cellularity, by a small B-cell lymphoma with an immunophenotype identical to the flow cytometry study "F25001746" (CD20+, CD5-, CD10-)
- **Immunohistochemistry:**
Positive for CD20, CD79a, and BCL2, and negative for CD5, BCL6, CD10, Cyclin D1, SOX11, and MUM1
Presence of 5% plasma cells, polytypic on immunohistochemistry for light chains
- **Molecular:**
Normal karyotype, no CXCR4, MYD88, or NOTCH1 mutation
GNB1 gene mutation identified

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Diagnosis

- Tumor board 27.08.2025:
 - “The integration of the morphological and flow cytometry results reasonably rules out follicular lymphoma, CLL, and mantle cell lymphoma.
There are no specific arguments in favor of lymphoplasmacytic lymphoma (plasma cells are polytypic).
 - **Conclusion : Clinically significant marginal zone lymphoma**
 - **Acquired angioedema due to C1 esterase inhibitor deficiency (C1INH-AAE)**

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Acquired angioedema due to C1 esterase inhibitor deficiency

- A rare disorder with an estimated prevalence of 1:600,000
- Typically presents after the fourth decade of life without family history of angioedema
- Mechanism : accumulation of bradykinin, a vasodilator, resulting in angioedema without urticaria

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Acquired angioedema due to C1 esterase inhibitor deficiency

- C1INH-AAE is most associated with lymphoproliferative disorders (LPDs), particularly low-grade B-cell subtypes (B-LPDs)
- Patients do not commonly present with constitutional symptoms nor other overt symptoms associated with LPD, hence posing a diagnostic challenge
- Treating the underlying B-LPD is important as this commonly leads to improvement or resolution of the angioedema in parallel with normalization of the complement studies

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Treatment

- 6 cycles of rituximab (Truxima) and bendamustin
- Firazyr (icatibant) on-demand

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On demand treatment and Prophylaxis

- Treatment of the condition is based on studies using treatments for hereditary angioedema (HAE).
- These are not registered or approved for the treatment of C1INH-AAE.

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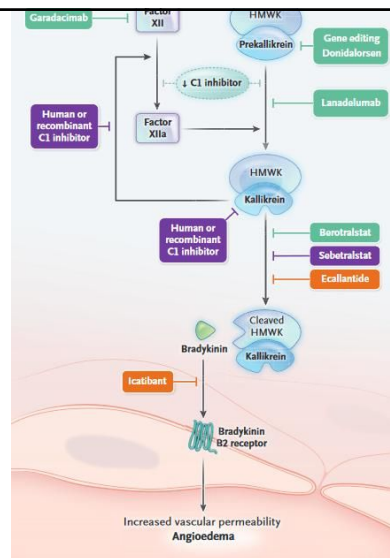


Figure 1. Pathways Leading to Increased Production of Bradykinin in Type 1 and Type 2 Hereditary Angioedema.

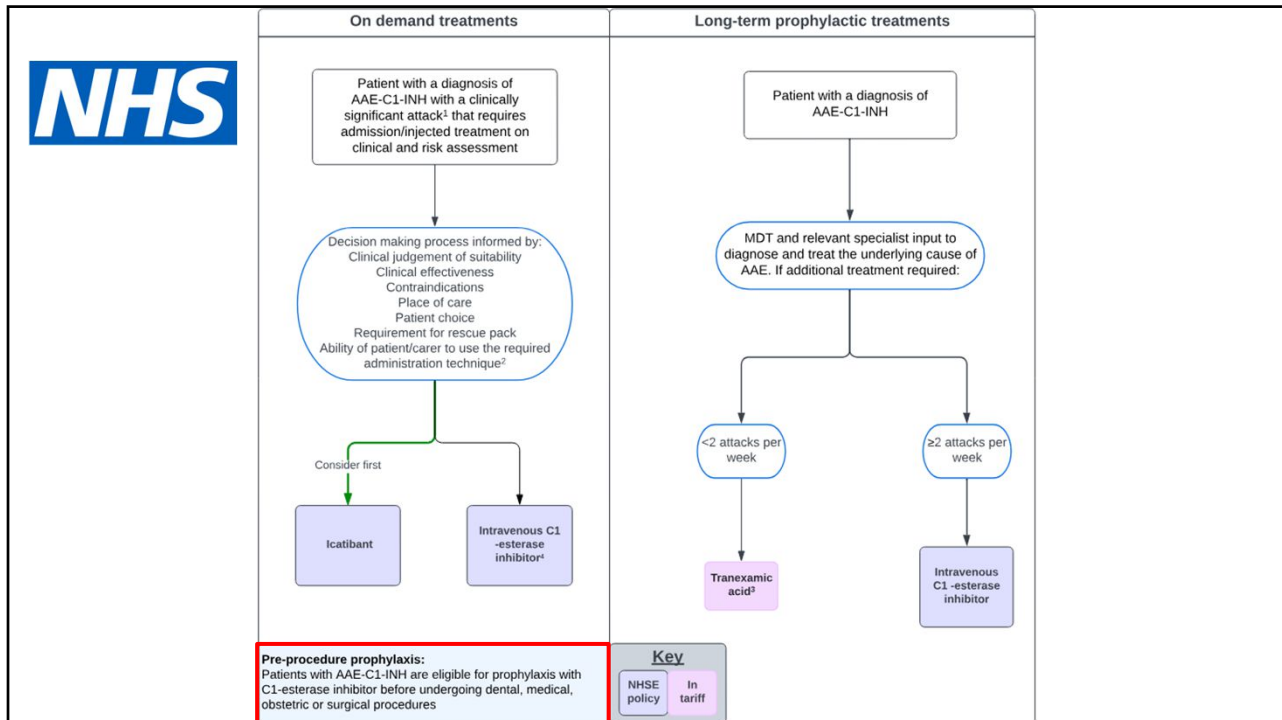
Shown are the mechanisms of action of drugs used to treat hereditary angioedema. Decreased levels of functional C1 inhibitor lead to dysregulation of the factor XIIa and kallikrein pathways. The green boxes indicate prophylactic treatments for hereditary angioedema attacks; the orange boxes, treatments for acute hereditary angioedema attacks; and the purple box, preparations for both prophylaxis and treatment of acute hereditary angioedema attacks. This simplified diagram does not include the complement or fibrinolytic pathways. HMWK denotes high-molecular-weight kininogen.

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On demand treatment and Prophylaxis

- Due to lack of data, recommendations specific to secondary angioedema are rare and based on expert consensus only

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Icatibant on demand?

RECOMMENDATION 9

We **recommend** that all patients have sufficient medication for on-demand treatment of at least two attacks and carry on-demand medication at all times

100% agreement, evidence level D

Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. *Allergy*. 2022; 77: 1961–1990. doi:[10.1111/all.15214](https://doi.org/10.1111/all.15214)

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Long-term Prophylaxis?

- Most recommended for HAE (evidence level A):
 - Berotralstat (Orladeyo®) per os
 - Lanadelumab (Takhzyro®) s.c.
 - Plasma derived C1 inhibitor
- Currently, there is not enough evidence to recommend any of these three treatment options over each other
- With our patient, no long-term prophylaxis was initiated in addition to hematologic treatment
 - (but to be re-evaluated depending on disease activity, burden, and control)

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Evolution

- 6 cycles of rituximab (Truxima) and bendamustin, initiated in September 2025
- Last angioedema attack : September 2025 (2 weeks after initiation of treatment)
- Angioedema-free for >4 months
- Laboratory findings as of January 2026
 - C4 0.02 (detectable)
 - C1 functional inhibitor 6 -> 33%

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References :

Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. *Allergy*. 2022; 77: 1961–1990.

doi:[10.1111/all.15214](https://doi.org/10.1111/all.15214)

Ng JY, Ooi M, Bennett SK, Rady K, Choi P, Lee WI, Cook MC, Randall KL, Pati NK. Acquired Angioedema Associated with Lymphoproliferative Disorders. *Case Rep Oncol*. 2024 Feb 23;17(1):329-336. doi: 10.1159/000536458. PMID: 38404406; PMCID: PMC10890797.

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