HAE In Pediatric Patients
Evaluation and Management Overview

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Clinical Onset of HAE Types 1/2 in Children

Genetic Defect

- HAE is an autosomal dominant disease
- The gene defect (SERPING1 mutation) of HAE-1/ 2 is already present at birth

Onset by Age

- Symptoms uncommon in neonates and infants
- Attacks can begin at any age - usually begin in childhood or adolescence – earliest occurrence reported at 4 weeks of age

Onset by Gender

- Female: half develop first attacks before the age of 12, and 90% by the time they are 23 years old.
- Male: 50% and 90% have first attacks before the age of 13 and 25, respectively.

Manifestation of HAE Attacks in Children

Angioedema, Abdominal Attacks

Most attacks in children manifest as skin angioedema. Abd attacks may go unrecognized as this is a common symptom in children

Upper Airway Edema and Asphyxia

Angioedema of the upper airway and asphyxia can occur more rapidly in children likely due to their smaller airway diameter

Attack Frequency and Severity

Attacks increase during puberty and adolescence. In general, the earlier the onset, the more severe the course

Prodromal Erythema Marginatum

It’s a prodromal sign seen more frequently in children (42%–58%), often misdiagnosed as urticaria leading to incorrect or insufficient tx

Diagnosis of HAE in Children

Offspring of HAE Patient	• HAE is autosomal dominant. Offspring of an HAE-1/2 patient has a 50% chance of inheriting the disease
Newborn	• All newborns with a positive family history should be screened to exclude HAE-C1-INH. Test children of HAE-1/2 parents as early as possible
Neonates	• Complement in umbilical cord blood of neonates are lower than maternal levels, leading to false positive (low) results. Complement in peripheral blood of children lack reference values.
Children < 1 Year Old	• C1–INH antigenic levels and/or functional activity in children with HAE, who are less than 1 year old, are generally low. C4 is not useful for diagnosis

Diagnostic Accuracy in Children With HAE

Genetic testing increases diagnostic reliability	• Genetic testing increases diagnostic reliability in children and is helpful when complement measurements are inconclusive and the genetic mutation of the parent is known
Repeat complement testing after age 1	• All early complement testing performed in patients before one year of age should be repeated after the age one
Prenatal diagnosis not common	• Prenatal diagnosis of HAE is not common in clinical practice (Mutations in parent are not detected (10%), identical mutations with different phenotypes, therapy improved QoL/disease control)

Guideline on Diagnosis of HAE in Children

Measurements of **C1–INH antigen (protein) level**, **C1–INH functional (activity) level**, and **C4 level** are recommended in children with angioedema without wheals.

RECOMMENDATION 20

We **recommend** testing children from HAE-affected families be carried out as soon as possible and all offspring of an affected parent be tested

98% agreement, evidence level D

Treatment of HAE in Children

Acute On-Demand Treatment

Short-Term Prophylaxis

Long-Term Prophylaxis

On-Demand and Short-Term Therapies

Acute On-Demand Treatment

- All pediatric HAE-1/2 patients require a on-demand therapy
- Approved therapies are generally effective and safe
- Action plan is needed in children
- Fluid replacement may be required

Short-Term Prophylaxis

- Similar to adults, pre-procedural prophylaxis is recommended for medical, surgical, and dental procedures associated with any mechanical impact to the upper airway and digestive tracts
- Plasma-derived C1–INH is the first-line option; short courses of attenuated androgens are second line

Guideline on On-Demand and Short-Term Treatment

On-Demand Therapy Should Be Available
Because Short-term Prophylaxis Is Not 100% Effective

RECOMMENDATION 21

We **recommend** C1 inhibitor or icatibant be used for the treatment of attacks in children under the age of 12.

94% agreement, evidence level A

Long Term Prophylaxis (LTP)

C1-INH

Indications are the same as in adults. Preferred therapy in children < 12 years old is pdC1-INH. Dosing needs to be adjusted by response

Antifibrinolytics

When C1–INH is not available, antifibrinolytics are preferred over androgens due to safety; efficacy may be variable

Androgens

NOT recommended in children. (masculinization, hypogonadism, menstruation irregularities, unfavorable behaviors, reduction in height)

Primary Prevention In Children

Triggers

Similar to adults, most attacks in children occur without an obvious trigger. Infections seem to be more common triggers for children

Vaccination

Compulsory and recommended vaccinations for children are safe. Prevention of infections (e.g., throat infections) may reduce frequency of attacks.

Contraceptives

Early initiation of oral estrogen-containing contraceptives should be avoided. In contrast, hormonal contraception with progesterone-only pills may benefit many young women with HAE

Activities and Stress

Strenuous physical activities and emotional challenges (stress) are common triggers in children. Restrictions of these activities should be individualized

Management in Children

Objectives	To normalize patient's lives, provide patients and families with appropriate information
	Educators, teachers, and health care personnel should receive written information (e.g., management of attacks, urgency of treating upper airway attacks)
	C1–INH or icatibant should be available at home, school, and travel including school field trips for emergency use
	An action plan for family and local hospital is essential. Therapies for emergency treatment should be available
	All HAE patients may receive human blood products. Vaccinations for hepatitis A and B are recommended. All should consider flu vaccine and other routine vaccinations.

References

- Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, Banerji A, Bara NA, Boccon-Gibod I, Bork K, Bouillet L, Boysen HB, Brodszki N, Busse PJ, Bygum A, Caballero T, Cancian M, Castaldo A, Cohn DM, Csuka D, Farkas H, Gompels M, Gower R, Grumach AS, Guidos-Fogelbach G, Hide M, Kang HR, Kaplan AP, Katelaris C, Kiani-Alikhan S, Lei WT, Lockey R, Longhurst H, Lumry WB, MacGinnitie A, Malbran A, Martinez Saguer I, Matta JJ, Nast A, Nguyen D, Nieto-Martinez SA, Pawankar R, Peter J, Porebski G, Prior N, Reshef A, Riedl M, Ritchie B, Rafique Sheikh F, Smith WR, Spaeth PJ, Stobiecki M, Toubi E, Varga LA, Weller K, Zanichelli A, Zhi Y, Zuraw B, Craig T. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022 Jan 10. doi: 10.1111/all.15214. Epub ahead of print. PMID: 35006617..
- Krogulska A, Lewandowska D, Ludwig H, Dąbrowska A, Kowalczyk A. Hereditary angioedema as a disease of different clinical courses and difficult diagnosis, particularly in children - a case report and literature review. Postepy Dermatol Alergol. 2021 Dec;38(6):1118-1121.

HAE In Pediatric Patients
Treatment Deep Dive

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Case: 4 Year Old Male With Recurrent Attacks

4 y/o male with HAE Type 1

Begins experiencing recurrent skin and soft tissue attacks

Local allergist orders Berinert 20 units/kg

Attacks persist and are now managed in ER with Berinert

However, this requires trip to ER (some distance from home)

Pt begins minimizing symptoms in part because of needle phobia

Pt and physician discuss options for ppx including (IV) C1-INH (Cinryze, off label Berinert) and (SC) C1-INH

Pt expressed an interest in (SC) C1-INH at home dosing. Appeal to insurance was approved.

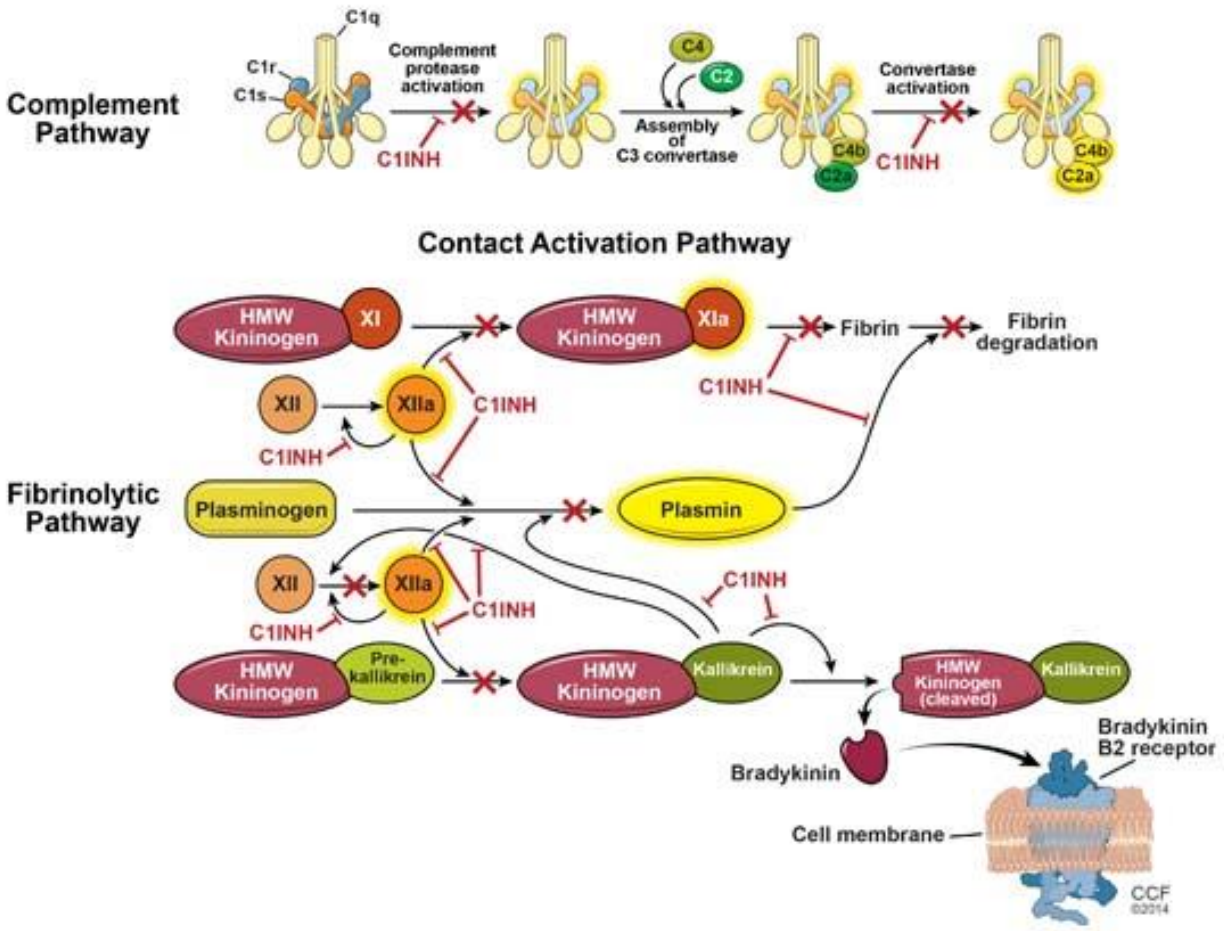
Attacks are reduced

Therapeutic Targets in HAE

Prophylaxis

(IV) C1-INH
(SC) C1-INH

Lanadelumab
Berotralstat



On demand

(IV) C1-INH
(IV) rhC1-INH

Ecallantide

Icatibant

Siles. Cleveland Clinic Center for Continuing Education 2017

HAE Treatment Approach

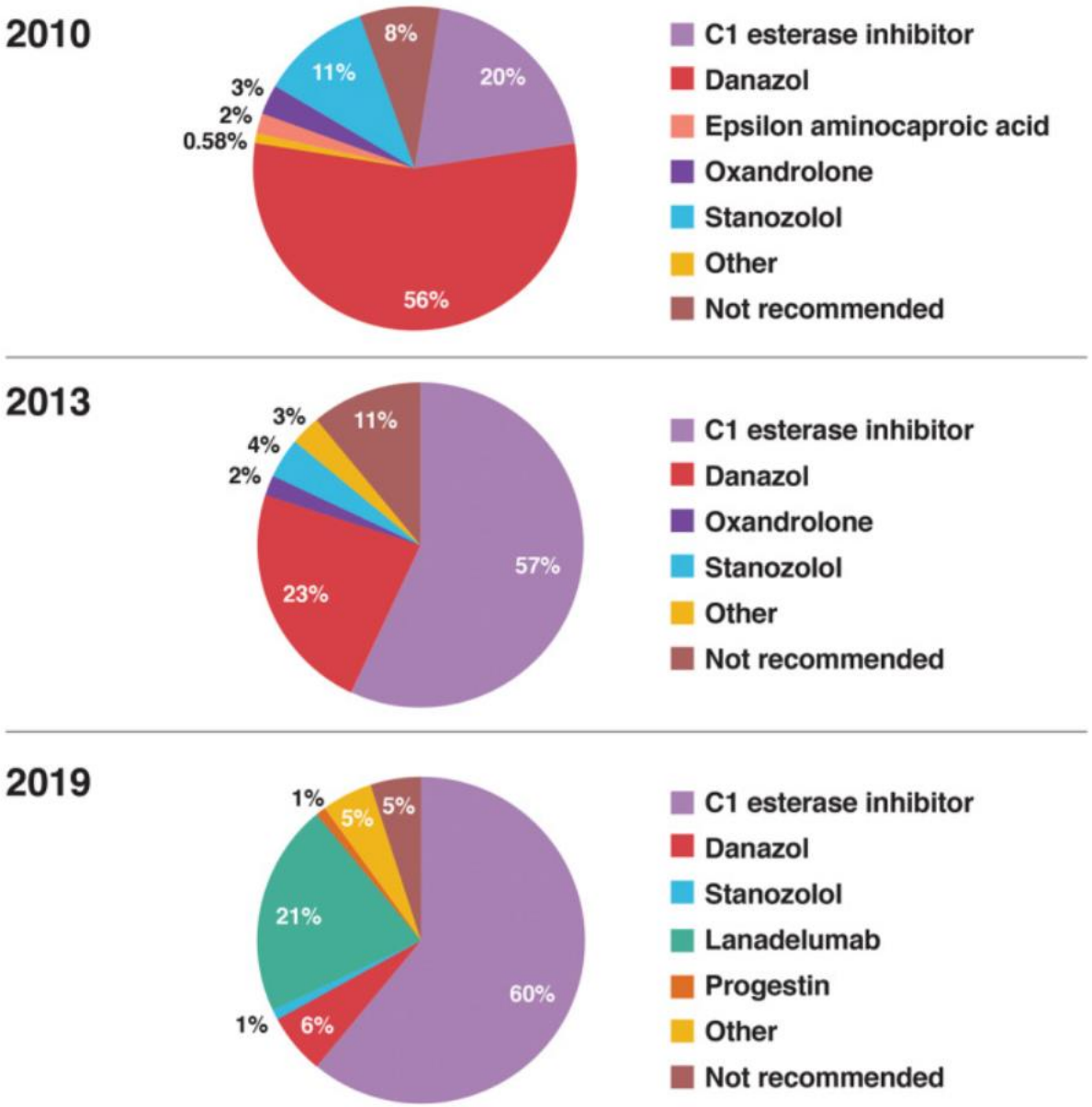
Core Principles

- On-demand acute therapy for all patients;
- Early treatment to prevent attack progression;
- Treatment of attacks irrespective of the site of swelling;
- Long-term prophylaxis (LTP) based on individualized decision-making

Changing Landscape

- The landscape of LTP has been transformed by the emergence of novel therapies.
- These treatments are anticipated to shift the management paradigm toward an expanded adoption of LTP

Busse et al. J Allergy Clin Immunol Pract 2021; 9(1):132-150



Long-term HAE prophylaxis medications reported by physicians as used "most frequently"

Riedl et al. Ann Allergy Asthma Immunol. 2021;126(3):254-272.

Acute Attacks - Approved Therapies for Pediatric Population

Drug	Class	Indicated Population	Dosing Route
Ecallantide	Kallikrein inhibitor	Adult Pediatric population ≥ 12 years old	SC
Icatibant	Bradykinin antagonist	Adult (USA) Pediatric population ≥ 2 years old (EU)	SC
C1INH (Berinert)	C1 esterase inhibitor (Plasma derived)	Adult Pediatric patients	IV
C1INH (Ruconest)	C1 esterase inhibitor (Recombinant)	Adult Adolescent population	IV

US Prescribing Information

Ecallantide - A Kallikrein Inhibitor for Acute Attacks

Pediatric Data	Significantly quicker onset of improvement, quicker time to complete resolution during acute attacks. Patient reported severity index showed marked decreases
	Studied in 25 patients aged 9 to 17. Effective in adolescents, with rapid symptom improvement. No unexpected safety issues were identified.
	Requires administration and monitoring by a health care professional

MacGinnitie et al. Pediatrics (2013) 132 (2): e490–e497.

Icatibant - A Bradykinin Antagonist for Acute Attacks

Adult Data	Cutaneous or abdominal attacks: significantly reduced median times to ≥50% reduction in symptom severity (2.0 vs 19.8 hrs), onset of primary symptom relief (1.5 vs 18.5 hrs), or almost complete symptom relief (8.0 vs 36.0 hours). A shorter time to initial symptom relief (0.8 vs 3.5 hrs).
	Laryngeal attacks: median time to 50% or more reduction in symptom severity was 2.5 hrs (icatibant) and 3.2 hours (placebo).
	No icatibant-treated subject required rescue medication before symptom relief occurred. Icatibant was effective and generally well tolerated in subjects with acute HAE attacks.

Lumry et al. Ann Allergy Asthma Immunol. 2011;107(6):529-37

Icatibant - A Bradykinin Antagonist for Acute Attacks

Pediatric Data EU	32 patients aged 2 years to younger than 18 years were categorized as children and adolescents
	The median time to onset of symptom relief (earliest time posttreatment to 20% or more improvement in composite symptom score) was 1.0 hour, the same for children and adolescent
	Treatment-emergent AEs are all mild or moderate. GI symptoms were most common. Injection-site reactions affected most patients, but almost all resolved by 6 hours

Farkas et al. J Allergy Clin Immunol Pract. 2017; 5(6):1671-1678.e2

C1 Esterase Inhibitor (Berinert) for Acute Attacks

Pediatric Data	Plasma derived C1 INH. Indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks in adult and pediatric patients
	It was evaluated in 12 patients aged 10 to 16 years in placebo-controlled studies with open-label extensions as well as in 18 patients (age 5 to 11 years) from a registry study
	The safety profile in the pediatric population was similar to that observed in adults.

Frank et al. Pediatrics. 2016;138(5):e20160575.

C1 Esterase Inhibitor (Ruconest) for Acute Attacks

Pediatric Data	Recombinant C1 INH. Evaluated in an open-label, phase 2 study included children aged 2-13 years.
	20 children (aged 5-14 years; 73 HAE attacks) were treated. Median TOSR was 60.0 minutes. Median TTMS was 122.5 minutes.
	No withdrew from the study due to adverse events (AEs). No treatment-related serious AEs or hypersensitivity reactions reported; no neutralizing antibodies were detected.

Reshef et al. Pediatr Allergy Immunol. 2019;30(5):562-568.

Prophylaxis – Approved Therapies for Pediatric Population

Drug	Class	Indicated Population	Dosing Route and Frequency
Berotralstat	Kallikrein inhibitor	Adult Pediatric population ≥ 12 years old	Oral daily
Lanadelumab	Kallikrein inhibitor	Adult Pediatric population ≥ 12 years old	SC 2-4 weeks
C1 INH (Cinryze)	C1 esterase inhibitor (Plasma derived)	Adult Pediatric population ≥ 6 years old	IV 3-4 days
C1 INH (Haegarda)	C1 esterase inhibitor (Plasma derived)	Adult Pediatric population ≥ 6 years old	SC 3-4 days

US Prescribing Information

C1 Esterase Inhibitor (IV and SC) for Prophylaxis

Pediatric Population

- LTP labeling for C1INH(IV) (Cinryze), plasma derived, has been expanded from adults to patients aged ≥6 years in 2018
- A SC formulation of C1INH (Haegarda), plasma derived, was subsequently approved for the prevention of HAE attacks in patients aged ≥6 years

Clinical Trial Data

- In patients aged ≥12 years with ≥2 attacks/month, C1INH(SC) significantly lowered rate of HAE attacks. The majority (90%) of patients had a ≥ 50% reduction in HAE attacks. Onset of prevention occurred within 2 weeks
- Sustained efficacy without emergence of safety concerns long term

US Prescribing Information. Longhurst et al. N Engl J Med 2017; 376:1131-1140

Berotralstat – A Kallikrein Inhibitor for Prophylaxis

Clinical Trial	Approved as an oral medication to prevent attacks of HAE in adults and pediatric patients aged ≥12 years.
Included Pediatric Patients	In Phase 3 APeX-2 study of patients with type 1/2 HAE and ≥2 HAE attacks requiring treatment or causing functional impairment, Berotralstat significantly reduced attacks compared to placebo (1.31 vs. 2.35, $p<0.001$).
	In Part 2 of APeX-2, reductions in attack rates either continued or declined further with no new safety signals. Part 3 of Apex-2, a long-term open-label extension phase, is ongoing.

Zuraw et al. J Allergy Clin Immunol. 2021 Jul;148(1):164-172.e9.

Lanadelumab – A Kallikrein Inhibitor for Prophylaxis

Clinical Trial	In HELP study, eligible patients were aged ≥12 years old and had ≥1 HAE attacks per month
Included Pediatric Patients	Lanadelumab had an 87% reduction in monthly HAE attack rate compared to placebo ($p<0.001$). Onset of prevention occurred within 2 weeks and attack prevention sustained throughout the study
	The long-term open-label extension of the HELP study reported sustained efficacy with no new safety concerns.

Banerji et al. JAMA, 320(20), 2108–2121.

Treatment Guideline for Children – Acute Attack

WAO/EAACI 2021	Indications for on-demand therapies follow the same guidelines as in adults.
US HAEA 2020	Treatment with pdC1-INH is effective, well tolerated, and shows a good safety profile in pediatric patients
	During abdominal attacks, parenteral fluid replacement may be required due to increased susceptibility of children to hypovolemia and dehydration

Maurer et al. Allergy. 2022 Jan 10. Busse et al J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3

Treatment Guideline for Children – Long-Term Prophylaxis

WAO/EAACI 2021, US HAEA 2020

- Indications for first-line HAE LTP medications are the same in children.
- Plasma-derived C1INH is preferred; dosing may need to be adjusted by response. SC form of C1INH offers benefit.
- Androgens are not recommended in children and adolescents

New Approvals

- Therapy or pediatric indication approved in the US after the publication of guidelines (e.g., berotralstat)

Maurer et al. Allergy. 2022 Jan 10. Busse et al J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3

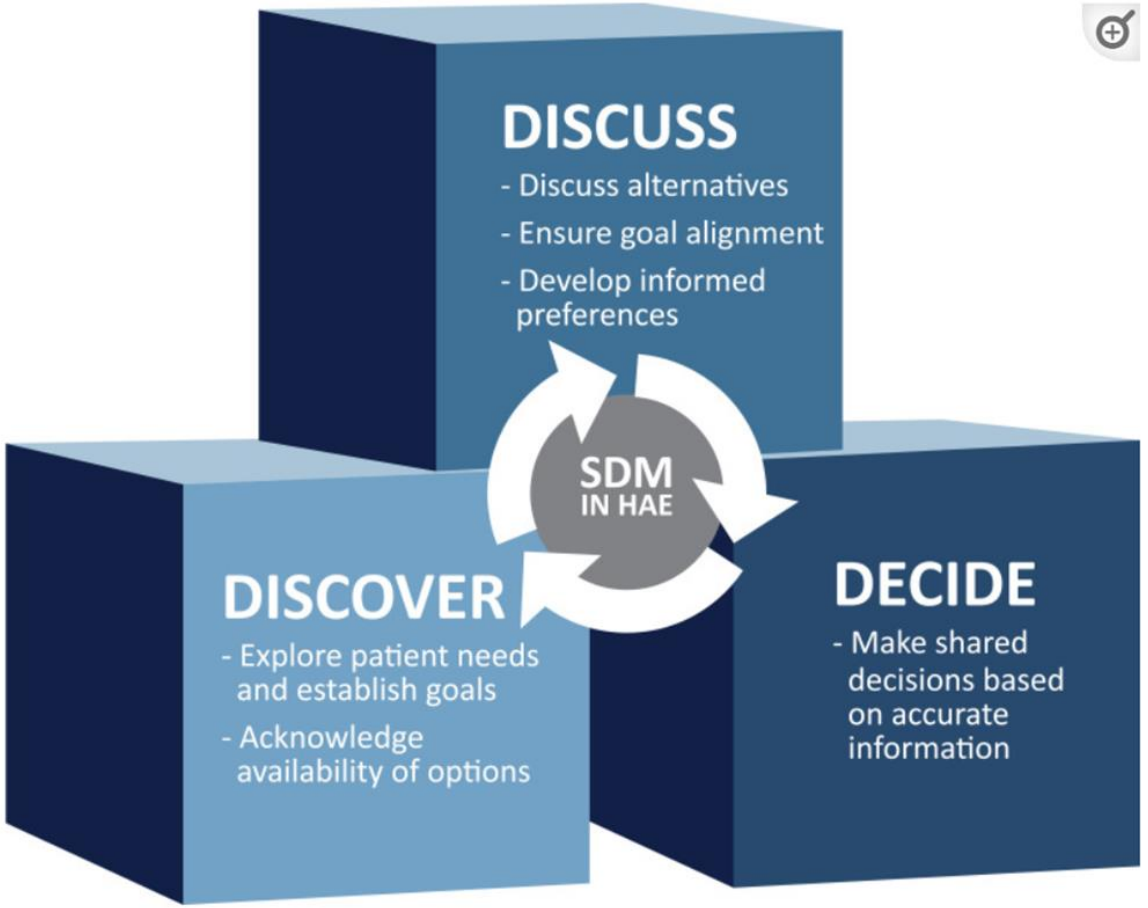
Key Decision Factors in Treatment

Clinical Aspects of Disease	Quality of Life Impact	Health-System and Treatment-Related Factors
- Overall disease burden/comorbidities - Angioedema attack frequency - Prior severe, debilitating, or life-threatening attacks	- Missed work or school - Interference with event planning (e.g., vacations, family occasions) - Inability to conduct ADL - Fear and anxiety about future attacks	- Access to urgent care - Benefit-risk and/or treatment burden of available HAE management options

Anderson et al. Clin Transl Allergy. 2022; 18;12(1):e12092.

Shared Decision Making in Treatment

- A three-phase "3D" model (Discover, Discuss, Decide)
- Treatment decision based on patient's needs, response to therapy, treatment goals
- A beneficial tool for optimizing therapy in HAE



Banerji et al. J Asthma Allergy. 2021; 14:119-125.

Specific Issues in Children

- Responsible adult including sports coach should be informed about HAE
- On-demand therapy should be made available at all points of care (home, school, camp)
- Effective therapy needs to be on hand in advance of symptom onset
- Key information includes an emergency plan to the network of responsible adults

Maurer et al. Allergy. 2022 Jan 10. Busse et al J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3