

Managing the transitioning HAE adolescent

- Meghan is a 15-year-old female with a family history of angioedema. She was diagnosed with HAE at the age of 1, and has a history of attacks
- This case describes a young patient who is navigating adolescence with HAE, who seeks advice from an angioedema specialist on treatment and considerations in HAE
- The following case is based on experiences from real patient cases, and content and images have been adapted for educational purposes

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*Images may not represent real patients

Case history and diagnosis

- Meghan has a family history of angioedema
 - Her father, grandfather, and uncle have all been diagnosed with HAE type I
 - She was diagnosed herself with HAE type I at the age of 7 months
- Her diagnosis was made at screening by assessing levels of C1-INH and functional C1-INH
 - C1-INH: 6.17 mg/dL
 - Functional C1-INH: 26.84%
 - Complement C4 level: 4.13 mg/dL
- Meghan was also diagnosed with pollinosis

1. To ensure optimal management and diagnosis of HAE, children with a positive family history must be tested as early as possible

A. True

B. False

1. To ensure optimal management and diagnosis of HAE, children with a positive family history must be tested as early as possible

A. True

B. False

Feedback

- With autosomal dominant inheritance, the offspring of a patient with HAE type I and type II stands a 50% chance of inheriting the disease¹
- Recent WAO/EAACI guidelines suggest:
 - Newborns with a positive family history are considered potentially affected until HAE-C1-INH is excluded and must be well observed and tested as early as possible, ideally before the onset of clinical manifestations, to ensure optimal management of the disease²
 - Therefore, testing children of parents with HAE type I and type II is recommended as early as possible¹
 - Until a full investigation for HAE is complete, all offspring of parents with HAE type I or type II should be considered to also have the disease¹

History of first HAE attack

- Meghan had been asymptomatic until the age of 7 when she started to experience abdominal attacks
- Her first attack involved swelling of the right hand lasting 2 days, accompanied by abdominal pain
 - She was taken to the emergency room and treated with intravenous pdC1-INH concentrate resulting in improvement within 1 hour
- Meghan then experienced 6 attacks that year, with 1 resulting in hospital admission



2. Alongside pdC1-INH, which other on-demand treatment options are available in Europe to treat pediatric patients with HAE?

- A. Recombinant C1-INH
- B. Icatibant
- C. Solvent detergent-treated plasma
- D. Ecallantide

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Feedback

- Approved on-demand treatment in pediatrics:¹
 - Intravenous pdC1-INH is recommended to treat patients of all ages with HAE*^{2,3}
 - Intravenous recombinant C1-INH is recommended to treat patients with HAE ≥2 years old⁴
 - Subcutaneous treatment with icatibant is recommended to treat patients with HAE ≥2 years old⁵
- When C1-INH and icatibant are not available, solvent detergent-treated plasma is preferred over fresh frozen plasma, but both are considered second-line treatment^{1,6}
 - In some countries, access to first-line HAE treatment for on-demand therapy is difficult as products are not registered or are unaffordable
 - There are limited available data on the efficacy and safety of solvent detergent-treated plasma and fresh frozen plasma in HAE
- Ecallantide is licensed for the use in adolescents in the US only^{1,7}

HAE, hereditary angioedema; C1-INH, C1-esterase inhibitor; pdC1-INH, plasma-derived C1-esterase inhibitor.

Indications for each product are according to European Prescribing Information. *Indicated for all ages with Berinert[®] and ≥2 years with Cinryze[®].

1. Maurer M. et al. *Allergy*. 2022. 2. [CSL Behring. Berinert 500/1500 Summary of Product Characteristics. 2021.](#) 3. [Takeda. Cinryze Summary of Product Characteristics. 2021.](#)

4. [Pharming Group N.B. Ruconest. Summary of Product Characteristics. 2021.](#) 5. [Takeda. Firazyr. Summary of Product Characteristics. 2021.](#)

6. Wentzel N. et al. *World Allergy Organ J.* 2019;12(9):100049. 7. [Takeda. Kalbitor prescribing information. 2020 16. Aug 2021](#)

Meghan's trips to the emergency room

- Since her diagnosis, Meghan has experienced:
 - Moderate-to-severe abdominal attacks
 - Many peripheral attacks
 - Some attacks involving the upper respiratory tract
- Her attacks typically lasted 3 days but some attacks, mainly peripheral, have lasted up to 5 days
- Most of the abdominal attacks, some of the peripheral attacks, and those attacks involving the respiratory tract have led to emergency room visits and, in some cases, admission for an observation period

3. What percentage of patients with HAE reported ≥ 1 HAE-related emergency room visit in 2018?

- A. 0–20%
- B. 21–40%
- C. 41–60%
- D. 61–80%
- E. >81%

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Feedback¹

- A non-interventional, cross-sectional, web-based survey of patients with a self-reported diagnosis of HAE type I or II in Australia, Canada and six European countries was conducted in 2018 to gain a comprehensive real-world understanding of the characteristics of HAE and its burden from the perspective of the patient
- A total of 242 patients completed the survey which reported that during the year prior to the survey, 37.6% of patients experienced ≥ 1 HAE-related emergency room visits
 - A total of 19.4% of patients experienced ≥ 1 HAE-related hospitalization
 - A total of 18.2% of patients experienced ≥ 1 HAE-related urgent care visit
 - These visits were most frequent for patients with more attacks in the last 6 months

4. With angioedema of the upper airway, asphyxia can ensue more rapidly in children than in adults

A. True

B. False

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A. True

B. False

Feedback

- Asphyxia as a result of angioedema of the upper airway can ensue rapidly in children, probably because of the small airway diameter¹
- Laryngeal edema may occur at any age, although young adults are at greatest risk^{1,2}
 - In adults, the interval between onset of symptoms and acute risk of asphyxiation is usually long enough to allow for use of appropriate emergency procedures²
- To prevent a fatal outcome, it is essential to instruct patients and their relatives about the first signs of laryngeal edema and the necessary procedures to follow in the case of an attack²
- The earliest occurrence of an attack was described in a 4-week-old boy³
- The earlier the onset of symptoms, the more severe the subsequent course of HAE type I and type II¹

HAE, hereditary angioedema.

1. Maurer M. et al. *Allergy*. 2022. 2. Bork K. et al. *Arch Intern Med*. 2003;163(10):1229–1235. 3. Bork K. et al. *Mayo Clin Proc*. 2000;75(4):349–354.

Treatment plan

- Following Meghan's continued HAE attacks, her treatment plan at this point included:
 - Intravenous pdC1-INH concentrate 20 IU/kg to treat acute attacks
 - Pre-procedural prophylaxis with intravenous pdC1-INH concentrate 20 IU/kg
- Meghan's attacks resolved within a few hours when treatment was administered early and lasted 24–36 hours when treatment was delayed

Initiation of long-term prophylaxis

- At the age of 10, Meghan was experiencing increased disease activity (9 attacks within a 6-month period)
- Her physician decided to switch her treatment:
 - LTP treatment with tranexamic acid (oral; 40 mg/kg/day; three doses)
 - Pre-procedural prophylaxis with intravenous pdC1-INH concentrate 20 IU/kg
- Her physician ruled out *Helicobacter pylori* and an abdominal ultrasound showed a fatty liver, but was of no connection to HAE

5. What LTP therapies are available in Europe to treat adolescent patients with HAE?

- A. pdC1-INH
- B. Icatibant
- C. Lanadelumab
- D. Berotralstat
- E. Tranexamic acid
- F. Androgens

5. What LTP therapies are available in Europe to treat adolescent patients with HAE?

- A. **pdC1-INH**
- B. Icatibant
- C. **Lanadelumab**
- D. **Berotralstat**
- E. Tranexamic acid
- F. Androgens

Feedback

- The preferred LTP therapy in children younger than 12 years old is pdC1-INH¹, although product indications vary depending on the manufacturer
 - The dosing interval and dose may need to be adjusted according to the individual response
 - Intravenous pdC1-INH is recommended in children ≥ 6 years old, depending on manufacturer²
 - Subcutaneous pdC1-INH is recommended in children ≥ 12 years old³
- Lanadelumab is recommended in children ≥ 12 years old⁴
- Oral treatment with berotralstat is recommended in children ≥ 12 years old⁵
- Icatibant is not recommended for LTP in pediatric patients with HAE; it is approved for on-demand treatment only⁶
- Androgens (e.g., danazol) are also not recommended for LTP in children and adolescents prior to Tanner Stage V, as they may interfere with natural growth and maturation¹
- Antifibrinolytics such as tranexamic acid (20–50 mg/kg) are preferred to androgens for pediatric patients because of their better safety profile; however, efficacy is questioned by many, and data in support of its use are not available¹

HAE, hereditary angioedema; LTP, long-term prophylaxis; pdC1-INH, plasma-derived C1-esterase inhibitor.

1. Maurer M. *et al.* *Allergy*. 2022. 2. [Takeda. Cinryze. Prescribing Information. 2021.](#) 3. [CSL Behring. Berinert 2000/3000 Summary of Product Characteristics. 2020.](#) 4. [Takeda. Takhzyro \(lanadelumab\). Summary of Product Characteristics. 2021.](#) 5. [BioCryst UK Ltd. Orladeoya \(berotralstat\). Summary of Product Characteristics. 2021.](#) 6. [Takeda. Firazyr. Summary of Product Characteristics. 2021.](#)

Self-administration treatment in pediatric patients

- Despite treatment with tranexamic acid, at the age of 11, Meghan experienced 11 attacks per year (including 4 upper airway attacks)
- With the aim of achieving better disease control, her physician suggested self-administration might be more suitable
- Meghan received training on how to self-administer intravenous pdC1-INH concentrate as well as subcutaneous icatibant acetate to treat her acute attacks
- As treatment was self-administered at the earliest sign of an attack, her attacks resolved within 1–3 hours after infusion, thus minimizing her hours of activity impairment and days away from school
- However, Meghan still preferred to avoid treating peripheral attacks; she also had concerns about administering at school or going home to administer and missing out at school

Meghan's challenging childhood

- Meghan was not able to participate in school activities in the same way as her peers
 - She felt unable to perform at the expected academic level and was anxious about the unpredictability of the disease and fear of attacks
- Her parents were worried about letting her participate in the same activities as her brother (e.g., short trips with school and spending holiday periods alone with her grandparents)
- During Meghan's exam period (when she was 12 years old), she experienced an increase in attack frequency due to stress
 - This resulted in her missing her exams and receiving poor academic results
- Meghan had missed many school days, felt anxious, and reported a poor quality of life
 - This led to her avoiding after-school activities and travelling without her parents' supervision

6. Which of the below factors can trigger HAE attacks in pediatric patients?

- A. Infections
- B. Mechanical trauma
- C. Emotional stress
- D. All of the above

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Feedback¹

WAO/EAACI guidelines suggest:

- As in adults, most attacks in children with HAE type I or type II occur without an obvious trigger
- Infections seem to be more common triggers of attacks in childhood
 - Compulsory and recommended vaccinations for children are safe, and the prevention of infections may reduce the frequency of attacks
 - Medicinal products that can cause edema as an adverse effect are less frequently used in children
- Early initiation of oral estrogen-containing contraceptives is increasingly common, may trigger attacks, and should be avoided. Hormonal contraception with progesterone-only pills may benefit many young women with HAE, or at least should not increase attack frequency
- Other triggers like strenuous physical activities involving mechanical trauma and emotional challenges (e.g., stress) are essential elements of childhood and adolescence
- Restrictions of suspected triggers should be individualized and sensibly applied, along with use of prophylaxis where necessary, with the aim of avoiding any limitations in activities and lifestyle
 - The aim of HAE type I and type II management at all ages is to normalize the lives of patients

Treatment during exam period

- Alternative treatment regimens were suggested during Meghan's exam period:
 - STP with intravenous pdC1-INH concentrate 20 IU/kg twice weekly during the exam period
 - Meghan saw an improvement in her academic results
 - STP with intravenous pdC1-INH concentrate 20 IU/kg before school trips or visiting grandparents alone*

pdC1-INH, plasma-derived C1-esterase inhibitor; STP, short-term prophylaxis.

**Berinert 500/1500 (C1-INH IV) is approved for the treatment and pre-procedure prevention of acute episodes of HAE. CSL Behring does not suggest or recommend the use of C1-INH (IV) in any way other than as described in the Summary of Product Characteristics.*

Long-term prophylaxis

- Despite her ongoing LTP with tranexamic acid as well as STP with intravenous pdC1-INH before stressful events that could trigger attacks, Meghan experienced 17 attacks in 6 months
- When it became available, she then switched to LTP subcutaneous pdC1-INH concentrate
 - Meghan was asymptomatic for 9 months and showed an improvement in her quality of life
- During the Coronavirus 2019 pandemic, she was not attending school and her disease activity declined significantly; thus, Meghan was switched back to on-demand therapy to treat acute attacks (occurring every 2–3 months)
- Meghan became more efficient at treating on demand and was able to get back into a normal daily routine, including attending fitness classes
 - Meghan's more normal daily routine including fitness classes eventually led to increased disease activity, with 1 attack occurring each week
 - At this point, she decided to switch back to LTP with subcutaneous pdC1-INH

7. Which factor(s) are the most important when developing a treatment plan for adolescents?

- A. Current frequency and severity of attacks
- B. Quality of life
- C. Patient preference
- D. Patient lifestyle and activity
- E. All of the above

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Feedback¹

WAO/EAACI guidelines suggest:

- Like adults, pediatric patients with HAE need to have a treatment action plan and on-demand therapy
 - It is important that an action plan is developed at diagnosis, even if the patient has not yet experienced attacks
- Physicians should monitor a patient's disease activity regularly (including frequency and severity of attacks) and adjust treatment regimens as needed
- Providing pediatric patients and their families with appropriate information is indispensable to support them to adopt a suitable lifestyle, good quality of life and to avoid complications
- Each treatment plan for an adolescent patient with HAE should be tailored to the patient's needs and preference, should be considered unique, and should be continuously reassessed
- Although it may be challenging to educate an adolescent patient on how to self-administer a non-oral treatment, it should be encouraged
- Teachers, and healthcare personnel responsible for the child should receive written information about the disease, with advice on the management of attacks, including the urgency of treatment for airway attacks

Summary and key messages I

- HAE can be dynamic during adolescence and the psychological impact of the disease should be proactively assessed
- Children with HAE need to have a treatment action plan readily available once diagnosed, even if the patient has not yet experienced attacks
- In Europe, C1-INH and icatibant are the only approved on-demand treatments for pediatric patients with HAE type I or type II
- The preferred LTP treatment in pediatric patients younger than 12 years of age is intravenous C1-INH (indications vary depending on manufacturer); however, dosing intervals and dosage may need to be adjusted according to the individual response
 - In order to achieve better disease control, adolescent patients can learn to self-administer non-oral therapies

Summary and key messages II

- Although most attacks in children with HAE type I or type II occur without an obvious trigger, infections seem to be more common triggers of attacks in children than in adults
 - Other triggers can include medicinal products, strenuous physical activities involving mechanical trauma and emotional stress
- In children, the impact of HAE attacks may become a challenge for school performance and attendance, and can impact the patient's quality of life
- It is important that teachers and school nurses are made aware of their disease and how to manage and treat attacks during school
- HAE management requires regular review throughout childhood and treatment plans should be continually reassessed to accommodate changes in symptoms and the growing independence of the child