

# Managing HAE in a severely affected patient

- Jane is a 34-year-old female with a BMI of 37 (obese)
- Her first HAE attack occurred when she was one year old
- In 2020 she experienced 77 HAE attacks in 9 months
- Today (April 2022), she is visiting the clinic for a routine check-up
- 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

# Patient history I

- When Jane was one year old, she experienced her first HAE symptoms
  - Her symptoms usually occurred in the gastrointestinal and peripheral regions, and were irregular in frequency
- At age 13, Jane was diagnosed with HAE type I
  - She encountered a long diagnostic delay since there was no family history until her mother first presented with symptoms at age 30
  - Her younger sister developed symptoms and was diagnosed at age 10, and her son presented symptoms and was diagnosed at age 2

1. What is the typical age for onset of HAE symptoms?

- A. 0–10 years
- B. 11–25 years
- C. 26–40 years
- D. 41–60 years
- E. 61 and above

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# Feedback: Onset of symptoms

- From birth, all patients with HAE type I or II have a defect in the *SERPING1* gene. However, symptoms of HAE rarely occur in newborns and infants
- Symptoms of HAE can first occur at any time, but most often begin in childhood or adolescence
  - Most patients have their first attack by the time they are 25, but this differs slightly between males and females

## Males

50% experience their first attack by 13  
90% experience their first attack by 25

## Females

50% experience their first attack by 12  
90% experience their first attack by 23

2. How long does it typically take for patients to be diagnosed with HAE?

- A. <1 year
- B. 1–5 years
- C. 5+ years

2. How long does it typically take for patients to be diagnosed with HAE?

A. < 1 year

B. 1–5 years

**C. 5+ years**

# Feedback: Diagnostic delay

- Diagnostic delay of HAE is common<sup>1</sup>
  - On average, diagnosis is delayed by 8.5 years from initial symptoms
  - Some studies have suggested delays of 13–20 years
- A delay in diagnosis can delay therapeutic intervention, resulting in patients experiencing worsened disease activity and a poor QoL<sup>2</sup>
- Sometimes patients with HAE are misdiagnosed, leading to inappropriate procedures e.g., patients with HAE may have unnecessary exploratory laparotomies, appendectomies, or other invasive procedures if presenting with an abdominal attack<sup>1</sup>



3. Which family members should be tested once a diagnosis of HAE is made?

- A. Grandchildren
- B. Children
- C. Siblings
- D. Parents
- E. Grandparents
- F. All of the above

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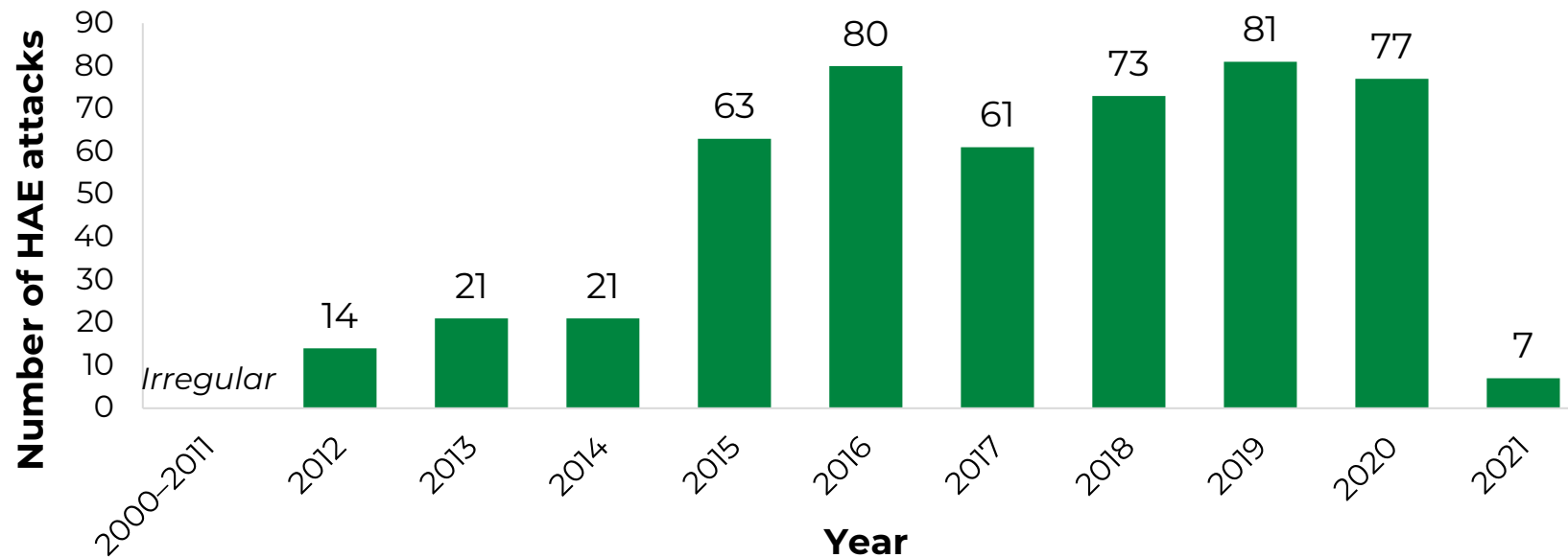
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- E. Grandparents
- F. All of the above**

# Feedback: HAE in families

- Once a patient has been diagnosed with HAE-1/2, family members including grandparents, parents, siblings, children and grandchildren should be screened for HAE
- 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 disease
- To diagnose/screen for HAE-1/2, the updated international WAO/EAACI guidelines for the management of HAE recommend the following measurements:
  - Serum/plasma levels of C1-INH function
  - C1-INH protein levels
  - Complement C4 concentrations
- In addition, genetic testing such as sequencing the *SERPINC1* gene can be supportive in the diagnostic workup of HAE-1/2 patients

## Patient history II: Number of HAE attacks per year

- Since 2000, the frequency of Jane's HAE attacks began to fluctuate, ranging from irregular attacks to over 80 per year



## 4. What factors can contribute to variations in HAE attack frequency?

- A. Trauma
- B. Weight gain
- C. Stress
- D. Hormonal changes
- E. Medication

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**A. Trauma**

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**C. Stress**

**D. Hormonal changes**

**E. Medication**

# Feedback: Variation in HAE attack frequency I

- The frequency of HAE attacks can vary considerably between patients and within patients, from virtually never to twice weekly<sup>1-3</sup>
  - The earlier the onset of symptoms, the more severe the subsequent course of HAE-1/2
  - The severity and course of HAE varies greatly between patients; even among family members with the same genetic mutation<sup>4</sup>
- Correlations between different types of mutations and clinical phenotype is controversial; however, one study suggests that a single missense mutation in C1-INH may be associated with milder phenotype<sup>5</sup>

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

1. Maurer et al. *Allergy*. 2022;77:1961–1990; 2. Martinez-Saguer et al. *J Allergy Clin Immunol*. 2013. 131(2)Supp AB30; 3. Bygum et al. *Front Med (Lausanne)*. 2017;4:212; 4. Santacroce et al. *J Clin Med*. 2021; 10(9):2023; 5. Bors et al. *J Allergy Clin Immunol*. 2013;131(6):1708–1711..

# Feedback: Variation in HAE attack frequency II

- A variety of conditions and events are known to trigger HAE attacks (i.e., trauma associated with dental, medical or surgical procedures, estrogen-containing oral contraceptive agents, estrogen hormone replacement therapy, ACE inhibitors and stress etc.)<sup>1</sup>
  - Attack frequency can be unpredictable with most attacks not prompted by triggers
- WAO/EAACI guidelines recommend that all patients should be educated about triggers that may induce attacks<sup>1</sup>
- In order to individualize and optimize the treatment of HAE patients, physicians need to understand their patients (i.e., severity/frequency of attacks, disease activity and the impact of the disease on QoL)<sup>2</sup>
  - Patient-reported outcome measures for assessing attack severity and frequency are available and valuable tools



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## Patient history III: Jane's medications

- Since her diagnosis with HAE, Jane has been treated with various on-demand treatments including:
  - pdC1-INH
  - Icatibant
  - rC1-INH
- However, on-demand treatment does not address attack frequency

5. Only severe HAE attacks affecting the upper airway need to be treated

A. True

B. False

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A. True

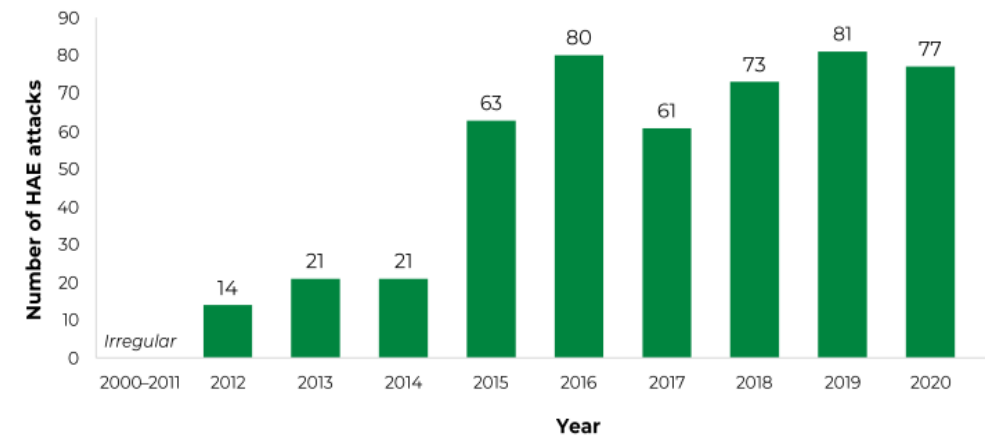
**B. False**

# Feedback

- WAO/EAACI guidelines recommend that on-demand treatment should be considered to be used to treat all HAE attacks, including:<sup>1</sup>
  - Attacks of the upper airways
  - Abdominal attacks
  - Peripheral attacks
- In patients with HAE, upper airway attacks can be life-threatening and thus the WAO/EAACI guidelines recommend that any attack affecting or potentially affecting the upper airway is treated<sup>1</sup>
- Peripheral attacks may also be associated with pain and dysfunction<sup>1,2</sup>
- Abdominal attacks can be sudden and painful and can often be misdiagnosed leading to unnecessary surgery<sup>3</sup>
- To improve treatment response, HAE attacks should be treated with on-demand therapy as early as possible<sup>1</sup>

## Patient history III: Jane's medications continued..

- To reduce the frequency of her attacks and improve her QoL, Jane was prescribed LTP treatments including:
  - Tranexamic acid (between 2001–2014)
  - Attenuated androgens (in 2006, but terminated due to side effects)
  - rC1-INH (in 2015 she was enrolled in a clinical trial)
- However, she still experienced a high number of HAE attacks and had significant impairment in her QoL
- At her last visit, Jane was prescribed SC C1-INH LTP in an attempt to provide effective prevention of attacks and improve her QoL



6. The goals of treatment in HAE have recently been defined as achieving complete control of the disease and normalizing patients' lives. Which factors should be considered when assessing the extent to which these goals have been achieved on a given management plan? (select all that apply)

- A. The number of attacks experienced by a patient in a given time period
- B. The proportional reduction in the number of attacks
- C. The requirement for rescue medication in a given time period
- D. The number of Emergency Department visits or hospitalizations
- E. The number of days of sick leave and the hours of activity impairment in a given time period
- F. All of the above

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# Feedback

- The 2021 update of the international WAO/EAACI guideline for the management of HAE recommend that the goals of treatment in HAE are to achieve total control of the disease and to normalize patients' lives<sup>1</sup>
- It is acknowledged that this can currently only be achieved by long-term prophylaxis, aimed at reducing the burden of disease by preventing attacks<sup>1</sup>
- A Delphi initiative recently examined the factors that should be considered when assessing disease control and normalization of the patient's life. The factors for which consensus was achieved were:<sup>2</sup>
  - The requirement for rescue medication in a given time period
  - The number of attacks experienced by a patient in a given time period
  - The proportional reduction in the number of attacks
  - The number of Emergency Department visits or hospitalizations
  - The number of days of sick leave in a given time period
  - The number of hours of activity impairment in a given time period
- Additionally, the mean length of attack-free period should be considered when assessing whether the life of a patient with HAE is normalized<sup>2</sup>



7. What factors should be considered in the decision to initiate long-term prophylaxis in a patient with HAE? (select all that apply)

- A. Disease activity
- B. Gender
- C. Availability of healthcare resources
- D. Patient preference
- E. Disease burden

7. What factors should be considered in the decision to initiate long-term prophylaxis in a patient with HAE? (select all that apply)

**A. Disease activity**

B. Gender

**C. Availability of healthcare resources**

**D. Patient preference**

**E. Disease burden**

# Feedback

- WAO/EACI guidelines recommend that all patients with HAE should be evaluated for LTP treatment at every visit, at least once a year taking into consideration:<sup>1</sup>
  - The patient's disease activity
  - The patient-specific burden of disease
  - The availability of healthcare resources
  - Failure of control by appropriate on-demand therapy
  - Patient preference

## 8. What are the recommended first-line treatments for LTP in adults with HAE?

- A. pdC1-INH
- B. Lanadelumab
- C. Berotralstat
- D. Attenuated androgens
- E. Tranexamic acid

8. What are the recommended first-line treatments for LTP in adults with HAE?

- A. **pdC1-INH**
- B. **Lanadelumab**
- C. **Berotralstat**
- D. Attenuated androgens
- E. Tranexamic acid

# Feedback

In adult patients:

- Long-term prophylactic (LTP) treatment aims to reduce and prevent the overall occurrence of angioedema attacks, with reduced disease and treatment burden<sup>1,2</sup>
- pdC1-INH IV or SC is a recommended first-line treatment for LTP<sup>2</sup>
  - The SC route may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1-INH compared to LTP with intravenous C1-INH, allowing for better symptom control
- Lanadelumab and berotralstat are recommended first-line therapies for LTP<sup>2</sup>
- Androgens should only be used as second-line LTP treatment due to associated adverse events<sup>2</sup>
- Antifibrinolytics such as tranexamic acid are not recommended for LTP, and are primarily used when first-line therapies are not available and androgens are contraindicated<sup>2</sup>

First-line	pdC1-INH, lanadelumab and berotralstat
Second-line	Attenuated androgens
Not recommended	Tranexamic acid

# At today's appointment...

- Jane is visiting for a routine check-up
  - It is now over 12 months since the initiation of long-term prophylaxis with SC C1-INH and she has not had an HAE attack yet!
  - As a result of disease control, she has become more active, lost weight and reduced her BMI



She has more control over her disease



She is happy with her treatment



Her QoL is improved



Her weight and BMI has decreased

9. What patient-reported outcome measures are available to evaluate a patient's disease activity, impact and control?

- A. Angioedema activity score (AAS)
- B. Hereditary angioedema activity score (HAE-AS)
- C. Angioedema QoL questionnaire (AE-QoL)
- D. Hereditary angioedema QoL questionnaire (HAE-QoL)
- E. Angioedema control test (AECT)
- F. All of the above



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- E. Angioedema control test (AECT)
- F. All of the above**

# Feedback<sup>1,2</sup>

- Patients treated with LTP should be monitored regularly to assess disease activity, impact and control to inform optimization of treatment dosages and outcomes
- A number of validated patient-reported outcome measures are available to help monitor patients. These include:
  - **Angioedema activity score (AAS) or hereditary angioedema activity score (HAE-AS)**
    - Assesses disease activity through the documentation of attack frequency
  - **Angioedema QoL questionnaire (AE-QoL) or hereditary angioedema QoL questionnaire (HAE-QoL)**
    - Assesses the impact of HAE on QoL
  - **Angioedema control test (AECT)**
    - Assesses HAE disease control by evaluating the frequency of symptoms, QoL impairment, unpredictability of episodes and the level of control achieved by current therapy

HAE, hereditary angioedema; LTP, long-term prophylaxis; QoL, quality of life.

1. Bork et al. *Allergy Asthma Clin Immunol.* 2021;17(1):40. 2. Maurer et al. *Allergy.* 2022;77:1961–1990.

# Take-home messages

- HAE is an unpredictable disease
  - Attack frequency can vary considerably between and even within patients
  - Symptoms vary widely in location, and severity, even within a family
- It is recommended that all patients should be educated about triggers that may induce attacks
- Treatment strategy must be evaluated frequently and adjusted individually for each patient
  - WAO/EAACI guidelines recommend that *“all attacks are considered for on-demand treatment”*
  - WAO/EAACI guidelines recommend *“evaluating patients with HAE for LTP at every visit, taking disease activity, burden, and control as well as patient preference into consideration”*<sup>1</sup>
  - Regular use of validated patient-reported outcome measures can help assess the need to amend a patient’s treatment plan
- Patients with HAE that experience unpredictable and/or multiple attacks often have an impaired QoL
  - Using suitable treatment strategies to reduce disease activity can reduce the overall burden of disease and help to improve a patient’s QoL