Follow-up and management of hereditary angioedema in specific conditions

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In The
Name Of
GOD

Hereditary angioedema in Women

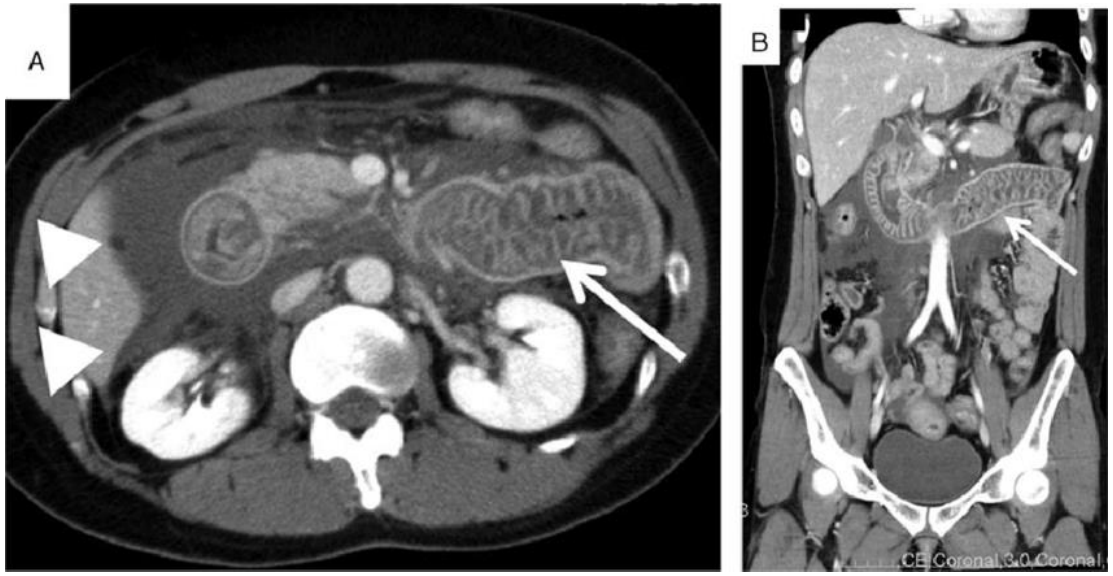
- Hereditary angioedema
- HAE-C1INH
  - Type1: C1 inhibitor deficiency
  - Type 2:C1 inhibitor dysfunction
  - SERPING1 gene mutations
  - C1-INH-HAE generally affect men and women in similar proportion.
- HAE-nl-C1INH
  - affects mainly women
  - men are mainly asymptomatic carriers
  - Mutation in coagulation factor XII, plsminogen, angiopoietin 1, and kininogen1, unknown
  - Exacerbation by increased exposure to estrogen (pregnancy, combined OCP drugs, ..)

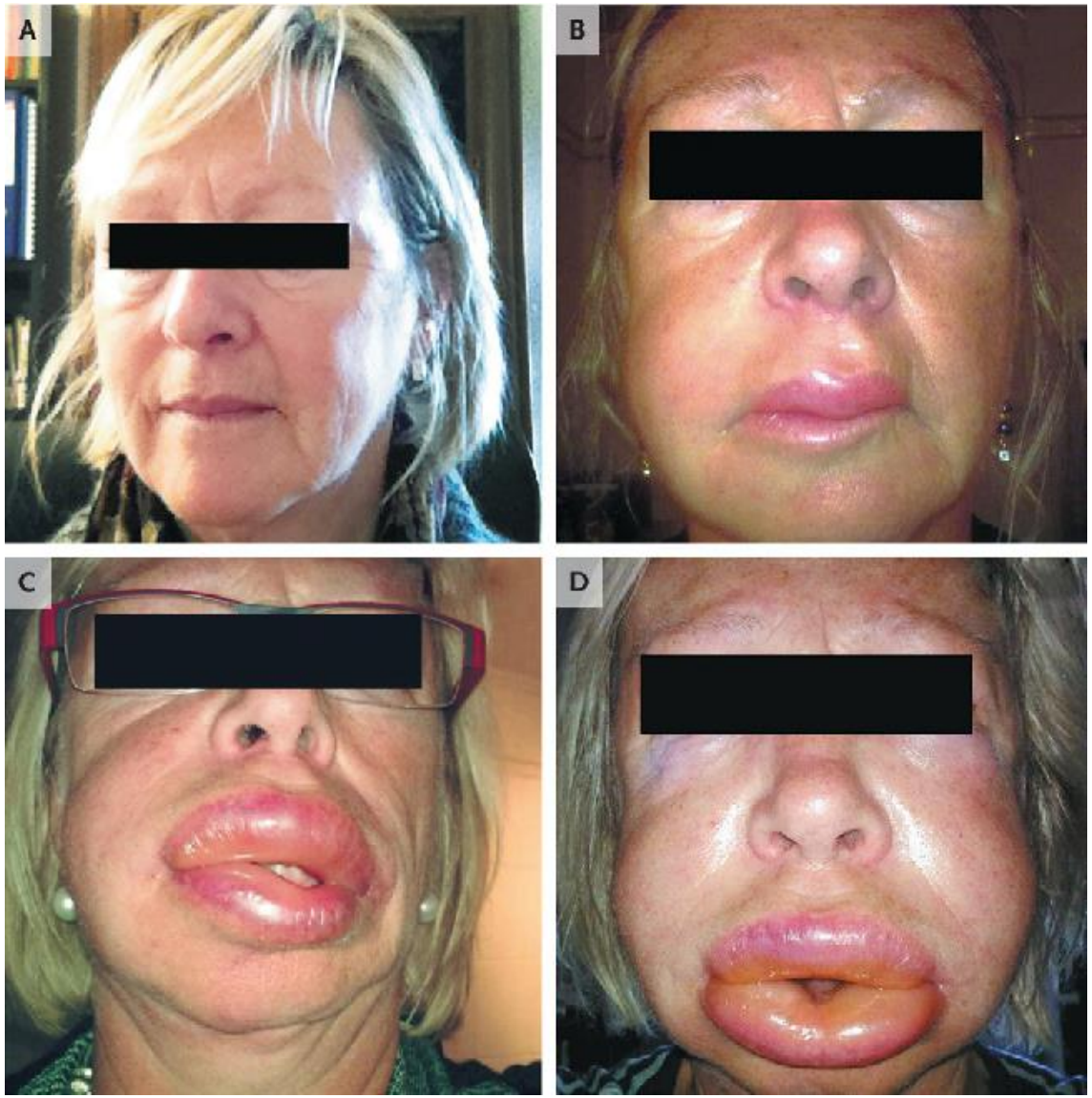
- Female sex hormones role in HAE:
  1. Women experience more attacks
  2. Women experience sever attacks
  3. In one cohort study by Bouillet of 150 women with HAE 62% had Worsened the disease during puberty, 80% worsened while taking estrogen-containing oral contraceptive, menstruation and ovulation trigger HAE attacks, progestin-only OCs reduce the frequency of attacks
  4. Exacerbation of attacks by initiation of estrogen in Turner's syndrome or during menopause
  5. High proportion of HAE-nlC1-INH begin the 1st symptom by initiating estrogen-containing Ocs or become pregnant for 1st time, or exacerbation by Ocs or pregnancy
  6. Women of C1-INH-HAE are high risk of polycystic ovary syndrome

Clinical presentation of HAE in women with C1-INH-HAE

- Majority of attacks in skin of the extremities or GI tract
- Face or genitalia attacks are less common , affect 2/3rd of patients in their lives
- C1-INH-HAE experience frequent abdominal attacks
  - Sever crampy and colicky abdominal pain
  - If untreated, last 2-5 days
  - Hospitalization occasionally is necessary
  - 4.4% cause collapse and shock, sometimes lead to loss of consciousness
  - 20% cause unnecessary surgery

- Laryngeal edema
  - Fewer than 1% of C1-INH-HAE attacks
  - Half of patients experience it
  - Can be fetal





Clinical presentation of HAE in women with HAE-nl C1-INH

- Later mean age of symptom onset (30 vs 14 years)
- More frequent swelling in the larynx, lips, face and tongue
- Less frequent swelling of abdomen compared to C1-INH-HAE

Triggers of HAE attacks

- Estrogen
- trauma such as dental work and medical procedures
- Repetitive work such as typing or yard work
- Sexual activity
- Emotional stress
- Infections
- Use of medications (ACE-inhibitor, estrogen, NSAIDs)

But most attacks occur without an identifiable trigger.

Treatment options

- On demand medication
  - Given at the onset of swelling to terminate attacks
  - Plasma-derived C1-INH (Berinert, Cinryze), ecallantide (kalbitor), icatiband (firazyr) , recombinant C1-INH (Ruconest)
  - Regional availability, regulatory approvals and/or cost barriers may prevent access to some medications, so less proven therapies may have a role, including FFP

Treatment options

- Long-term prophylaxis
  - For prevention care
  - Attenuated androgens such as danazol and stanazolol (benefits: oral administration, good efficacy in most patients and low cost; cautions: side effects, safety and tolerability, no effect in reversing the attack; should be used at the lowest effective dose, not exceeding 200mg/day for danazol or 2mg/day for stanazolol ; contraindicated in pregnancy and lactation and younger than 16 years of age)
  - Pd-C1INH, drug of choice in pregnant and lactating women ; if not tolerated or available, tranexamic acid or FFP on demand may be used;
  - Tranexamic acid (antifibrinolytic)
  - Lanadelumab , fully human monoclonal antibody to kallikrein,300mg/sc/every 2w if no attack occurs after 6 m reduce the dose to 300mg/every 4w; haven't been studied in pregnancy
  - Berotralstat , plasma kallikrein inhibitor, 150mg/day orally use; haven't been studied in pregnancy

Table 1. Drugs/products used in the treatment of hereditary angioedema.

	Availability[1]	Mechanism of action	Route of admin	Role(s) in HAE management[2]	Comments
HAE-specific agents					
Plasma-derived C1-INH concentrate (Berinert®)	US, EU, AU	Replacement of C1-INH	iv.	Acute attacks Short-term prophylaxis Long-term prophylaxis	No known safety issues specific to female patients. Treatment of choice for acute attacks in pregnant and breast-feeding women and those trying to conceive [37]
Plasma-derived C1-INH concentrate (Cinryze®)	US, EU, AU	Replacement of C1-INH	iv.	Acute attacks Short-term prophylaxis Long-term prophylaxis	No known safety issues specific to female patients. Treatment of choice for acute attacks in pregnant and breast-feeding women and those trying to conceive [37]
Ecallantide (Kalbitor®)	US, EU, AU	Selective inhibition of plasma kallikrein	sc.	Acute attacks	No known safety issues specific to female patients. No human safety data available for use in pregnancy or breast-feeding
Icatibant (Firazyr®)	US, EU, AU	Bradykinin-B2 receptor antagonist	sc.	Acute attacks	No known safety issues specific to female patients. No human safety data available for use in pregnancy or breast-feeding
Recombinant human C1-INH (Ruconest®)	US, EU	Replacement of C1-INH	iv.	Acute attacks	No known safety issues specific to female patients. No human safety data available for use in pregnancy or breast-feeding
Attenuated androgens					
Danazol (Danocrine®) Stanozolol (Winstrol®) Oxandrolone (Oxandrin®)	US, EU, AU (all)	Increased hepatic synthesis of C1-INH and increased degradation of kinins	Oral	Short-term prophylaxis Long-term prophylaxis	Not recommended in pregnant/lactating women or patients ≤16 years of age [37]; possible side effects of particular relevance to female patients include virilization and menstrual irregularies, mainly with long-term use. Lowest effective dose should be used [38]. Liver function tests should be performed every 6 months; liver biopsies every 12 months (every 6 months in patients using danazol doses >200 mg/day or equivalent) [35]
Antifibrinolytics					
ε Aminocaproic acid (Amicar®) Tranexamic acid (Lysteda®, Cyklocapron®)	US, EU US, EU, AU	Inhibition of plasmin	Oral, iv.	Not routinely recommended if other agents are available; option for long-term prophylaxis during pregnancy if C1-INH unavailable	No known safety issues specific to female patients. Tranexamic acid more widely available
Other					
Fresh frozen plasma	US, EU, AU	Contains C1-INH	iv.	Alternative when other therapies are not available	No known safety issues specific to female patients

[1]Availability/licensing status shown for the US, European Union (EU) and Australia (AU). Availability in other regions may differ.
[2]Based on HAE Consensus Guidelines [36,38–39].
iv.: Intravenously; HAE: Hereditary angioedema; sc.: Subcutaneously.

- Pregnancy’s effects on the frequency of HAE attacks:
  - angioedema episodes may become more frequent, less frequent or remain unchanged
- Distinguishing abdominal HAE attack from other complications of pregnancy:
  - Detection of free peritoneal fluid and edema of the intestinal wall (by abdominal ultrasound)
- Some reports suggest highest attack frequency in the first trimester and declines in the second and third, whereas others found in the third trimester.
  - reflect changes in estrogen levels especially in relation to progesterone levels

- Carrying a fetus with the HAE mutation is associated with a higher frequency of third-trimester attacks.
- The frequency of attacks during one pregnancy does not predict the frequency in subsequent pregnancies .
- Long-term prophylaxis should be considered for women with: histories of miscarriage, high-risk pregnancies and those with frequent, severe attacks
- Medication dosage is suggested to be the same as in nonpregnant patients .
- When available, pdC1-INH is generally recommended over other treatment options during pregnancy.

Labor & delivery

- Vaginal delivery is preferred
- surgery or general anesthesia with endotracheal intubation may provoke an attack
- HAE attacks are uncommon during vaginal delivery (6–8%), therefore routine prophylaxis against an HAE attack is not recommended.
- In case an attack does occur, acute treatment (preferably pdC1-INH) should be available
- short-term prophylaxis with pdC1-INH before vaginal delivery is advisable If the patient has a history of severe attacks or genital attacks secondary to trauma or her attacks have been frequent during the third trimester, before forceps delivery or vacuum extraction.

- In cesarean delivery, pdC1-INH should be administered as short-term prophylaxis.
- Epidural anesthesia is preferred
- Emergency procedures should not be delayed if pdC1-INH is not immediately available.
- Patients may experience an increased frequency of HAE attacks during the postpartum period, specially if she had experienced perineal swelling after delivery.
- Close follow-up for 72 h after delivery is recommended, and the patient should be informed of the treatment plan in the event of an HAE attack.

Termination of pregnancy

- Short-term prophylaxis before surgical abortion is recommended .
- alternatively, the procedure may be carried out without prophylaxis, provided that acute treatment is immediately available.
- A case report described successful medical abortion by using tranexamic acid for short-term prophylaxis; pdC1- INH was available but not needed.

Genetic counseling

- Genetic counseling should be offered to all patients with HAE, with establishment of the pedigree and education regarding inheritance.
- Prenatal diagnosis can be done if the parent’s genetic mutation is known.
  - Chorion villus sampeling after 10 w of gestation
  - Amniotic fluid sample after 15 w of gestation
  - preimplantation genetic testing, If IVF has been performed
- Diagnostic testing for HAE in infants has low reliability, test should be repeated after 1 y of age

Lactation

- increased frequency of HAE attacks can occur, possibly with increased serum prolactin levels, and discontinuing lactation might reduce the frequency of attacks.
- Tranexamic acid is excreted into breast milk and should not be used in patients who are breastfeeding.
- Anabolic androgens should be avoided during lactation, because of their potential adverse effects in children.
- Consensus guidelines recommend pdC1-INH for on-demand or prophylactic therapy of HAE in lactating women.

Contraception

- In as many as 80% of women, use of estrogen-containing oral contraceptives precipitates the onset of HAE attacks in a previously healthy patient or exacerbates previously diagnosed HAE.
- Study:
  - Use of progestin-only ocs reduced the frequency of attacks in 45 (81.8%) of 55 women with HAE. In 11 patients, improvement while on progestin-only OC enabled them to discontinue long-term prophylactic therapy.
- Antigonadotropic agents (lynestrenol, nomegestrol and chlormadinone acetate) were more effective than low dose progestin-only pills (L-norgestrel, norgestrienone and desogestrel).
- IUDs are generally well tolerated by women with HAE . Short-term prophylaxis before insertion is not considered necessary, but treatment for an attack should be available.

- For emergency contraception, a progestin-only agent should be used, and estrogen containing agents should be avoided.
- Barrier method of contraception have been found safe.
- **Menstruation**
- attacks are reported to be triggered by menses in 35% and by ovulation in 14%
- Diagnosing an abdominal HAE attack during menses
  - the primary differential is pelvic endometriosis;
  - severe abdominal pain, ascites or intestinal edema, and improvement after administration of an HAE treatment suggests HAE

Menopause

- 32% reported symptom worsening,13% reported improvement and 55% reported no change
- Estrogen replacement therapy is contraindicated
- Progesterone and progestins are alternatives for treatment of hot flashes.
- Nonhormonal treatments for the symptoms of menopause are not known to trigger HAE attack.

Infertility

- Fertility is unaffected by HAE, however no data are available regarding the effect of HAE medications on fertility .
- Short-term prophylaxis is recommended before salpingography.
- If intrauterine insemination or IVF is attempted, estrogen induced by injectable gonadotropins may trigger an HAE attack. Therefore if possible IVF should be performed during spontaneous cycles when estradiol levels are lower and less likely to cause hyperstimulation.
- Short-term prophylaxis with pdC1-INH should be provided before procedures that might trigger an attack, and should be used in the event of an attack.

Gynecologic surgery

- Before intubation or major procedures of any type, short-term prophylaxis should be considered (androgens for 5 days prior to the procedure or pdC1-INH).
- If pdC1-INH is used, it should be administered as close to the procedure as possible, preferably within 1 h and definitely within 6 h . Expert guidelines recommend 10–20 units/kg, with a second dose of equal amount available during the procedure.

• Gynecologic cancer

Androgens have potential adverse effects in patients with breast cancer, therefore they should be avoided if possible in patients with HAE and breast cancer.

Antiestrogens may have some agonistic effects on estrogen receptors; tamoxifen has been reported to exacerbate HAE symptoms and should be used with caution; an aromatase inhibitor may be preferable.

Androgens are not contraindicated in endometrial or cervical cancer.

Executive summary

Hereditary angioedema

- Hereditary angioedema (HAE) is a rare, chronic disorder characterized by sporadic, painful and debilitating edematous attacks which are usually spontaneous but can be triggered by physical trauma, emotional stress or hormonal fluctuation.
- HAE symptoms appear more prevalent among females than males, and HAE can complicate, or be aggravated by, a number of obstetric/gynecologic aspects of women's health.
- Treatment strategies include acute treatment of individual attacks, long-term prophylaxis, short-term prophylaxis prior to a potential triggering event or some combination of these.

Pregnancy

- Pregnancy has the potential to change the frequency of HAE attacks.
- The use of plasma-derived C1-inhibitor (pdC1-INH) during pregnancy is recommended by recent expert guidelines when treatment is necessary.
- Attenuated androgens are contraindicated during pregnancy.

Labor/delivery/postpartum

- Vaginal birth is preferable to cesarean delivery in women with HAE.
- HAE prophylaxis during delivery is not recommended as a routine practice, but might be considered in certain cases depending on personal risk factors.
- Epidural anesthesia is preferable to intubation to reduce the risk of a potentially fatal laryngeal attack.
- Lactation can increase the frequency of HAE attacks; pdC1-INH is recommended for women who desire to breastfeed.

Contraception

- Estrogen-containing birth control pills often exacerbate HAE and should be avoided, while progestin-only contraceptives may lessen attack frequency.
- IUDs are generally well tolerated by women with HAE.

Future perspective

- Recent years have witnessed a marked increase in the number of treatment options available for HAE and additional therapies are expected to emerge over coming years.
- The underlying pathophysiology of HAE, including various subtypes, continues to be characterized more fully, including the role of estrogen in some variants. Ongoing discoveries in this area may improve treatment strategies in women with HAE.
- Optimal management of female patients with HAE will continue to require close collaboration between HAE-treating physicians and women's health professionals.

Hereditary angioedema in children and adolescents

- HAE-C1INH is rare and usually present at childhood or adolescence.
- Diagnosis as early as possible and optimal management of the disease is optimal. Differentiation from histaminergic angioedema, acute abdomen, viral gastroenteritis is important.
- Triggers : stress, physical truma, infection, changes in estrogen levels and certain food (not always determined)
- Testing:
  - Genetic study
  - C4 level (low level of C4, having high level of specificity and sensitivity /C4 test alone is not sufficient for diagnosis)/ C1INH function and level
    - The tests results should take into account age-dependent normal value , especially before age of 1 year old

- Time of diagnosis:
  - Test for all patients with suspected hereditary angioedema due to symptoms or a known family history
  - Newborn with a positive family history are considered potentially affected until it is excluded. And must observed and tested as early as possible.
    - Check C4 , C1INH level and function from age of 4w on and verified the test at the age of 1 y.
    - Testing umbilical cord blood is not recommended as even in unaffected children, antigenic and functional C1INH cord blood levels are only approximately 70% & 62% of adult normal values.
    - Prenatal testing is not recomended?.

Therapeutic options

TABLE 1 Approval status and dosing of products for the treatment of HAE-C1-INH in German-speaking countries (as of September 2019)

Products (application mode)	Countries	Home therapy	Dosing per age-group		
			On-demand	Short-term prophylaxis	Long-term prophylaxis
pdC1-INH					
Berinert® 500/1500[a] (iv)	Germany + Austria[b]	Possible	≥0 y: 20 IU/kg	0-<18 y: 15-30 IU/kg ≥18 y: 1000 IU	–
	Switzerland	Possible	≥0 y: 20 IU/kg	≥0 y: 20 IU/kg	–
Berinert® 2000/3000 (s.c.)	Germany + Austria	Possible	–	–	≥12 y: 60 IU/kg 2x/wk
	Switzerland	–	–	–	–
CINRYZE® (iv)	EU	Possible	2-11 y (10-25 kg): 500 IU ≥2 y (>25 kg): 1000 IU	2-11 y (10-25 kg): 500 IU ≥2 y (>25 kg): 1000 IU	6-11 y: 500 IU every 3-4 d ≥12 y: 1000 IU every 3-4 d
	Switzerland	Possible	≥6 y: 1000 IU	≥6 y: 1000 IU	≥6 y: 1000 IU every 3-4 d
rhC1-INH					
Ruconest® (iv)	EU	Possible	≥2 y: <84 kg: 50 IU/kg ≥84 kg: 4200 IU	–	–
	Switzerland	–	–	–	–

Products (application mode)	Countries	Home therapy	Dosing per age-group		
			On-demand	Short-term prophylaxis	Long-term prophylaxis
Icatibant					
Firazyr® (s.c.)	EU + Switzerland	Possible	2 -<18 y: 12-25 kg: 10 mg 26-40 kg: 15 mg 41-50 kg: 20 mg 51-65 kg: 25 mg >65 kg: 30 mg ≥18 y: 30 mg	–	–
Lanadelumab					
Takhzyro® (s.c.)	EU + Switzerland	Possible	–	–	≥12 y: 300 mg/2 wk[c]
Tranexamic acid					
Cyklokapron® (oral)	Germany	Possible	–	up to 3 × 1.5 g	up to 50 mg/kg daily[d]
	Austria	Possible	–	2-3 × 500 mg 2-3x/d[e]	2-3 × 500 mg 2-3x/d[e]
	Switzerland	Possible	–	25 mg/kg daily[e]	25 mg/kg daily[e]

- plasma-derived C1 inhibitor concentrates are considered the best option for on-demand treatment, for short- and long-term prophylaxis across all pediatric age-groups.
- For on-demand treatment of children aged 2 years and older, recombinant C1-INH and bradykinin-receptor antagonist icatibant are alternatives.
- For long-term prophylaxis in adolescents, the parenteral kallikrein inhibitor lanadelumab has recently been approved and can be recommended due to proven efficacy and safety.
- In many part of the world, attenuated androgens used as short and long term prophylaxis, but is not recommended in children any more.
- Antifibrinolytics (aminocaproic acid or tranexamic acid) are used in many part of the world for lack of better alternatives. They are less effective than androgen but safer.

- Pre pubertal children can usually be managed with on-demand therapies alone because HAE symptoms are generally less severe prior to puberty.
- The expanded availability of these therapies for HAE attacks has greatly reduced the number of children who require long-term prophylaxis.
- However, for those who do require preventative therapy, SC or IV pdC1-INH or oral tranexamic acid (TA) are commonly used.
- We suggest avoiding androgens in children who require long-term prophylaxis despite on-demand therapy

- Baseline laboratory studies:
  - Baseline study for hepatic and other organ function, due to potential need for chronic medication and for blood-borne illness. AST, ALT, total bilirubin, albomin, creatine kinase, blood urea nitrogen, creatinine, CBC, pregnancy testing, UA, HIV,HBV,HCV.
- Vaccinate against Hepatitis B in whom blood-derived product is needed in future.
- The long-term prophylaxis refers to the use of regular medication to reduce the burden of the disease.
- Goal of long-term prophylaxis is deem successful when symptoms are controlled to a level that is acceptable to that patient.

- Long-term prophylaxis treatments:
  - targeted therapies (pdC1INH, lanadelumab, berotralstat) and are generally more effective, less side effects and more expensive, 1st line long-term prophylaxis medications
  - non-targeted therapies (androgens and antifibrinolytic) ,less effective and more side effects

Therapy	Age-groups			
	0-<2 y	2-<6 y	6-<12 y	≥12 y
On-demand				
Products	• Berinert (iv)	• Berinert (iv) • CINRYZE (iv)[a] • Ruconest (iv)[b] • Firazyr (s.c.)	• Berinert (iv) • CINRYZE (iv) • Ruconest (iv)[b] • Firazyr (s.c.)	• Berinert (iv) • CINRYZE (iv) • Ruconest (iv) • Firazyr (s.c.)
General	• Always treat attacks affecting the neck and head area • Treat as early as possible • Children < 6 y: also treat attacks at all other body locations • Children ≥ 6 y: consider attacks at all other body locations for on-demand treatment • Keep emergency medicine available and within easy reach at all times			
Short-term prophylaxis				
Products	• Berinert (iv)	• Berinert (iv) • CINRYZE (iv)	• Berinert (iv) • CINRYZE (iv)	• Berinert (iv) • CINRYZE (iv)
General	• Recommended for all medical procedures with significant tissue traumatization and surgical interventions in neck and head area • For procedures where short-term prophylaxis is not given, keep emergency C1-INH concentrate available • Administer as shortly as possible before the planned procedure			
Long-term prophylaxis				
Products	• Not recommended	• None approved	• CINRYZE (iv)	• Berinert (s.c.) • CINRYZE (iv) • Takhzyro (s.c.)
General	• For long-term prophylaxis treatment decision, consider frequency of attacks, disease burden, and impairment of everyday life			

Hereditary angioedema in elderly

- Symptoms often begin by age 11-13 years and worsen during puberty, but attacks can occur at any age and recur throughout life.
- acquired form of C1-INH deficiency: presents in older patients (ie, age >40 years) without a family history of angioedema and is associated with underlying disorders or autoantibodies against C1-INH in most cases.
  - Check C1q (C1q is normal in 30%)
  - Evaluation of lymphoproliferative disorder and hematologic malignancy

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Elderly versus younger patients with hereditary angioedema type I/II: patient characteristics and safety analysis from the Icatibant Outcome Survey

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Abstract

Background: Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is characterized by recurrent swelling in subcutaneous or submucosal tissues. Symptoms often begin by age 5–11 years and worsen during puberty, but attacks can occur at any age and recur throughout life. Disease course in elderly patients is rarely reported.

Methods: The Icatibant Outcome Survey (IOS) is an observational study evaluating the safety, tolerability, and efficacy of icatibant. We conducted descriptive analyses in younger (age < 65 years) versus elderly patients (age ≥ 65 years). Here, we report patient characteristics and safety-related findings.

Results: As of February 2018, 872 patients with C1-INH-HAE type I/II were enrolled, of whom 100 (11.5%) were ≥ 65 years old. Significant differences between elderly versus younger patients, respectively, were noted for median age at symptom onset (17.0 vs 12.0 years), age at diagnosis (41.0 vs 19.4 years), and delay between symptom

C1-INH-HAE attacks may occur at any age and recur throughout a patient's lifetime. Treatment of acute attacks is a lifelong necessity and can pose unique challenges for elderly patients. Presence of age relate pharmacokinetic and pharmacodynamic changes, coupled with the high likelihood of comorbid conditions for which multiple medications are required, underscores the importance of monitoring the safe use of medication in this population.

Elderly patients with C1-INH-HAE were signifcantly older at diagnosis and had greater delay in diagnosis than younger patients. Our analysis found similar AE rates in icatibant-treated elderly versus younger patients.

Our analysis did not identify any new or unexpected safety concerns of medication in this population.

Long-term safety and efficacy of subcutaneous C1-inhibitor in older patients with hereditary angioedema

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ABSTRACT

Background: Patients aged 65 years and older with hereditary angioedema (HAE) owing to C1-inhibitor (C1-INH) deficiency may have an altered response to treatment and are at higher risk for treatment-related adverse events (AEs) because of comorbidities and polypharmacy.

Objective: To investigate the safety and efficacy of subcutaneous C1 esterase inhibitor (C1-INH) in patients aged 65 years and older treated in an open-label extension of a phase 3 trial.

Methods: Eligible patients (≥4 attacks for more than 2 consecutive months) were randomized to receive twice-weekly subcutaneous C1-INH with a dosage of 40 IU/kg or 60 IU/kg for 52 to 140 weeks. Safety end points and efficacy outcomes were evaluated for patients aged 65 years and above and younger than 65 years.

Results: Of the 126 patients treated, 10 were 65 years and older (mean age [range], 68 [65-72 years]). A total of 8 of 10 patients had multiple comorbidities, and 6 of these 10 patients were taking more than 5 non–HAE-related drugs concomitantly. AEs occurring in more than 1 patient included injection site bruising (n = 2, related), injection site pain (n = 2, related), urinary tract infection (n = 2, unrelated), and diarrhea (n = 2,

Patients aged 65 years and older with hereditary angioedema (HAE) owing to C1-inhibitor (C1-INH) deficiency may have an altered response to treatment and are at higher risk for treatment-related adverse events (AEs) because of comorbidities and poly pharmacies.Of the 126 patients treated, 10 were 65 years and older (mean age [range], 68 [65-72 years]). A total of 8 of 10 patients had multiple comorbidities, and 6 of these 10 patients were taking more than 5 none HAE related drugs concomitantly. AEs occurring in more than 1 patient included injection site bruising (n 2,related), injection site pain (n ;2, related), urinary tract infection (n: 2, unrelated), and diarrhea (n : 2,unrelated).

No thromboembolic events or cases of anaphylaxis were reported.

Comorbidities in hereditary angioedema

- C1INH regulate the classical and lectin pathways of the complement system, main regulatory protein of the contact system, inhibiting activated factor XII (FXIIa), kallikrein, and activated factor XI (FXIa).
- During angioedema attacks, there is an increased generation of thrombin, with signs of activation of both the contact and tissue factor coagulation pathways.
- Thus, chronic activation of the classical pathway of the complement system as well as the contact and coagulation systems may pave the way for comorbid conditions in HAE. Previous studies have shown a link between HAE and autoimmune diseases, in particular systemic lupus erythematosus (SLE), autoimmune thyroiditis and, other autoimmune disorders has been reported in HAE.

- Currently used prophylactic treatment options in HAE include substitution with recombinant or plasma-derived C1-INH as well as treatment with attenuated androgens, mainly danazol or oxandrolone.
- Side effects of attenuated androgens can contribute to comorbidities in HAE, since long-term use of danazol is associated with increases in atherogenic indices shuch as myocardial infarction, stroke, deep vein thrombosis, and other cardiovascular abnormalities .
- The risk of CVD was higher among HAE patients compared to controls. The cumulative incidence of CVD was significantly higher for the HAE cohort with differences being apparent between the third and sixth decades of life. When subgrouping HAE patients based on gender, middle-aged men (i.e. third to sixth decades of life) still had a higher risk.

- Hypertension and arterial and venous thromboembolic events were significantly increased.
- Hyperlipidemia, a risk factor for CVD, was twice as common in HAE patients compared to controls.

Diagnosis	Cases $n = 239$ (100%)	Controls 2383 (100%)	OR (95% CI)	p value
All cardiovascular diseases	53 (22.18%)	321 (13.47%)	1.83 (1.32–2.54)	<0.001
Arterial thrombosis/embolus	4 (1.67%)	6 (0.25%)	6.74 (1.89–24.06)	0.009
Cerebral infarction	4 (1.67%)	52 (2.18%)	0.76 (0.27–2.13)	0.604
Brain hemorrhage	1 (0.42%)	16 (0.67%)	0.62 (0.08–4.71)	0.642
Hypertension	36 (15.06%)	233 (9.78%)	1.64 (1.12–2.39)	0.013
Ischemic heart disease[a]	12 (5.02%)	98 (4.11%)	1.23 (0.67–2.28)	0.497
Pulmonary embolism	4 (1.67%)	21 (0.88%)	1.91 (0.65–5.62)	0.229
Venous thrombosis/embolus	19 (7.95%)	48 (2.01%)	4.20 (2.42–7.23)	<0.001
Deep vein thrombosis	4 (1.67%)	18 (0.76%)	2.24 (0.75–6.66)	0.138

- HAE patients showed increased risk for all autoimmune diseases.

Diagnosis	Cases *n* = 239 (100%)	Controls 2383 (100%)	OR (95% CI)	*p* Value
All autoimmune diseases	42 (17.6%)	273 (11.5%)	1.65 (1.15–2.35)	0.007
Blood and immune system[a]	1 (0.4%)	9 (0.4%)	1.11 (0.14–8.79)	0.922
Endocrine system[b]	18 (7.5%)	94 (3.9%)	1.98 (1.18–3.35)	0.02
Nervous system and the eye[c]	2 (0.8%)	23 (1%)	0.87 (0.20–3.70)	0.845
Gastrointestinal tract[d]	4 (1.7%)	56 (2.3%)	0.71 (0.25–1.97)	0.505
Skin[e]	9 (3.8%)	60 (2.5%)	1.52 (0.74–3.09)	0.251
Musculoskeletal system and connective tissue[f]	13 (5.4%)	56 (2.3%)	2.39 (1.29–4.44)	0.004
SLE	7 (2.9%)	1 (0.04%)	71.87 (8.80–586.7)	<0.001
Glomerulonephritis and nephrotic syndrome	2 (0.8%)	10 (0.4%)	2.00 (0.44–9.19)	0.362

- A two-fold higher prevalence of allergy, asthma, and atopic dermatitis was found (OR 2.19).
- No increased risk of cancer was seen among HAE patients compared with controls (OR 0.89).
- Brickman has been reported an increased prevalence of autoimmune diseases, 12% out of 157 individuals with HAE had autoimmune disease, including glomerulonephritis, Sjögren's syndrome, inflammatory bowel disease, thyroiditis, SLE, and rheumatoid arthritis.
- In HAE, the lack of functional C1-INH leads to chronic activation and consumption of C4. The resulting impaired classical pathway function in turn leads to a lack of C3b which is involved in the clearance of apoptotic cells which can result in production of autoantibodies. Autoantibodies and deposition of immune complexes into tissues are linked to several autoimmune diseases including SLE.

- Taken together, attention to the importance of awareness regarding thromboembolic and autoimmune disease among HAE patients. In particular among middle-aged men with regard to CVD and among middle-aged women with regard to autoimmune disease.
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Thank you for your attention