Disclosure of Conflicts of Interest

Marc Riedl, MD, MS

- **Research Support:** Biocryst, CSL Behring, Ionis, Pharming, Shire
- **Consultant**: Arrowhead, Biocryst, CSL Behring, Global Blood Therapeutics, Pharming, Salix, Shire
- **Speakers Bureau:** CSL Behring, Salix, Shire

Angioedema Attacks: An Old Problem

- Marcella Donati (1586)
  - *De medica historia mirabili.*
- Heinrich Irenaeus Quincke (1882)
  - *Monatshefte für praktische Dermatologie*, 1882;1:129-131.

H.I. Quincke

HEREDITARY ANGIO-NEUROTIC OEDEMA.1
WILLIAM OSLER
The American Journal of the Medical Sciences (1827-1924); Apr 1888; 95, 4; American Periodicals Series Online
pg. 362

HEREDITARY ANGIO-NEUROTIC ŒDEMA.[1]

BY WILLIAM OSLER, M.D.,

Osler: Hereditary Angio-Neurotic Edema

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HEREDITARY ANGIO-NEUROTIC ŒDEMA.[1]

BY WILLIAM OSLER, M.D.,

Briefly summarized, the affection in the family which I have studied has the following characteristics:

1. The occurrence of local swellings in various parts of the body, face, hands, arms, legs, genitals, buttocks, and throat. In one instance, possibly in two, death resulted from a sudden *œdema glottidis.*

2. Associated with the œdema, there is almost invariably gastro-intestinal disturbance: colic, nausea, vomiting, and sometimes diarrhœa.

3. A strongly marked hereditary disposition, the disease having affected members of the family in five generations.

HAE: Deficiency of C1 Esterase Inhibition

VOL. 35, JULY 1963 37 AMERICAN JOURNAL OF MEDICINE

A Biochemical Abnormality in Hereditary Angioneurotic Edema*

Absence of Serum Inhibitor of C′1-Esterase

VIRGINIA H. DONALDSON, M.D.† *and* RICHARD R. EVANS, M.D.

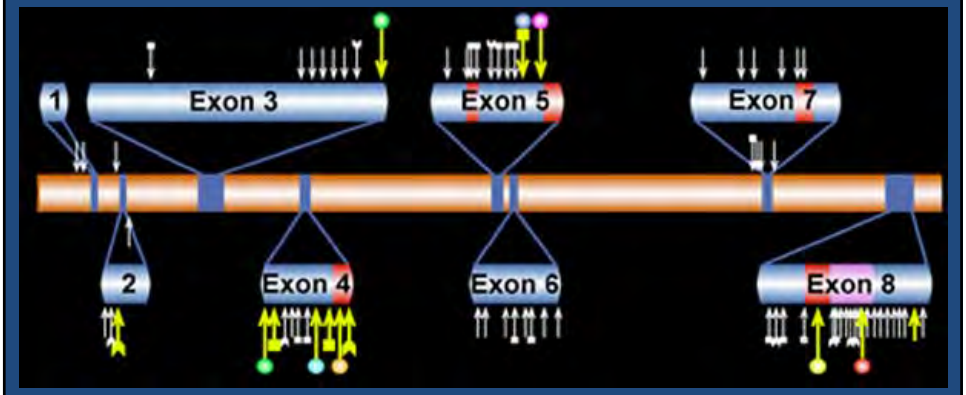
330 LANDERMAN ET AL. J. Allergy July—August, 1962

HEREDITARY ANGIONEUROTIC EDEMA

II. Deficiency of Inhibitor for Serum Globulin Permeability Factor and/or Plasma Kallikrein

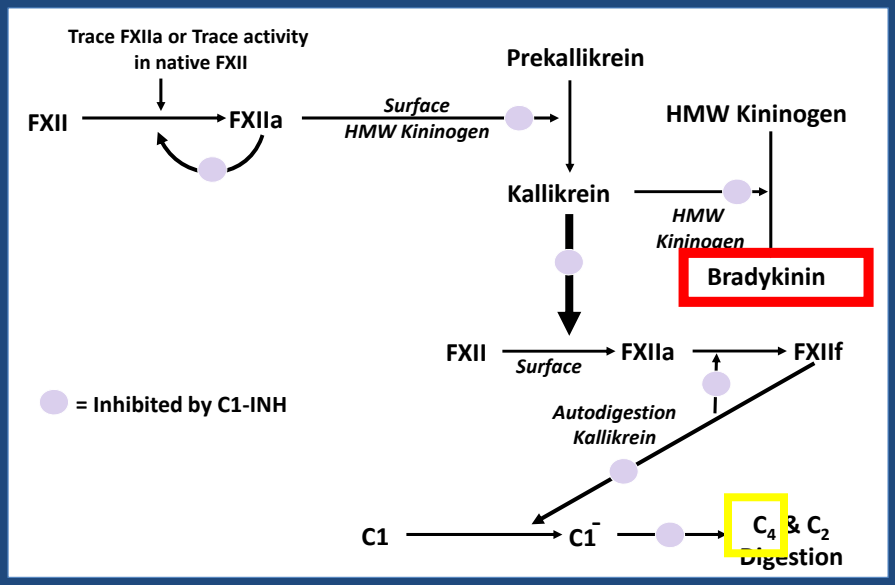
Nathaniel S. Landerman, Major, MC, USA. Marion E. Webster, Ph.D.,** Elmer L. Becker, Ph.D., M.D.,*** and Harold E. Ratcliffe, Colonel, MC, USA.**** Washington, D. C., and Bethesda, Md.*

HAE Caused by C1-INH Mutations

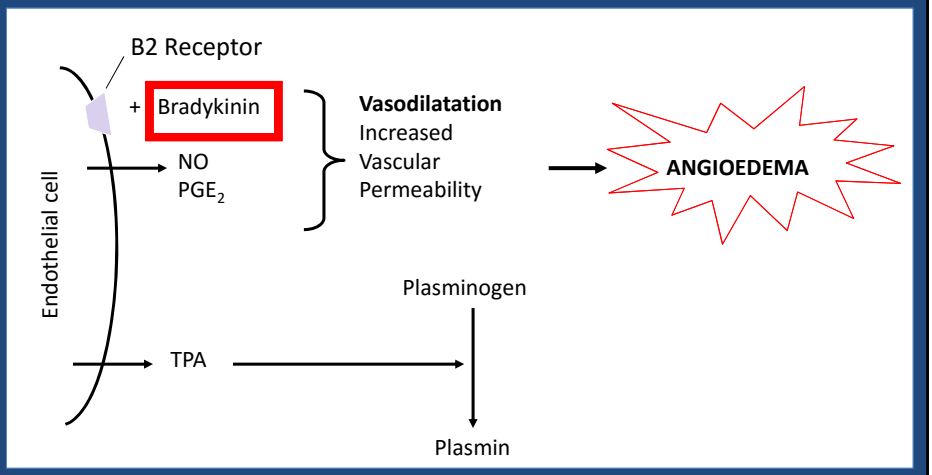


Zuraw BL, Herschbach J. *J Allergy Clin Immunol*. 2000;105:541-546.

Function of C1-INH



Activation of Endothelial Cells by Bradykinin



NO=nitric oxide; PGE_2=prostaglandin E_2; TPA=tissue plasminogen activator.

Zhao Y, et al. *Am J Physiol.* 2001;280:1821-1829.

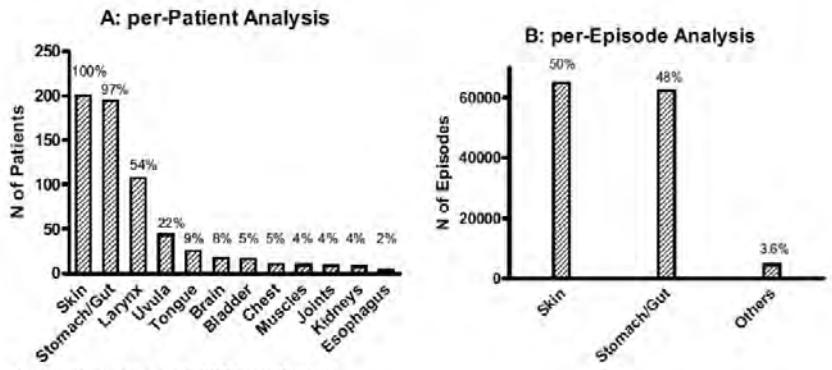
Types of HAE

- 3 documented types of HAE

	Type 1	Type 2	Type 3
Percent of all HAE	~85%	~15%	Rare
C4 Level	Low	Low	Normal
C1-INH antigenic level	Low	Normal	Normal
C1-INH antigenic function	Low	Low	Normal

Anatomical Location of HAE Symptoms

- 221 HAE patients
- 5736 patient-years of observation
- 131,110 angioedema attacks



Bork K, et al. *Am J Med*, 2006:119:267-274.

Hereditary Angioedema (HAE): Extremity Attacks

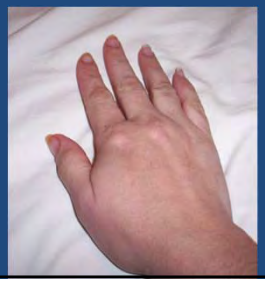
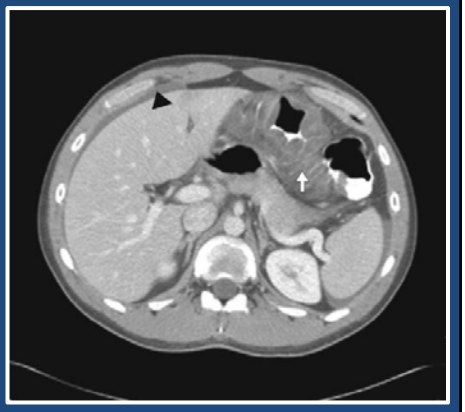


Photo from Frank MM.

Abdominal Attacks

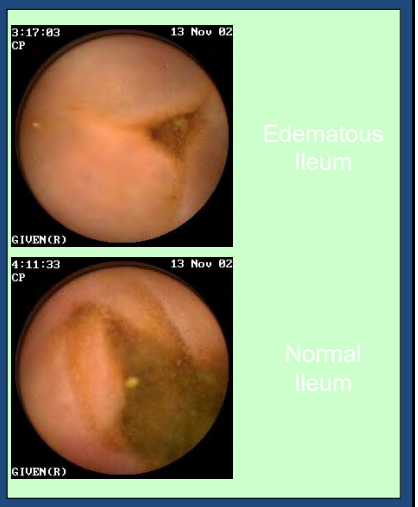
- Mild to severe pain
- Vomiting common; constipation/diarrhea may occur
- Fluid loss may lead to shock
- Abdominal distension, tenderness
- Symptoms mimic surgical emergencies, resulting in misdiagnosis and unnecessary surgery



Agostoni A, et al. *J Allergy Clin Immunol*. 2004.
Agostoni A, Cicardi M. *Medicine*.1992

HAE: Abdominal Attacks

Frank MM, et al. *Annals Int Med*. 1976



Courtesy of Dr. Marco Cicardi, personal archive.

Facial Edema in HAE

Photo from Frank MM

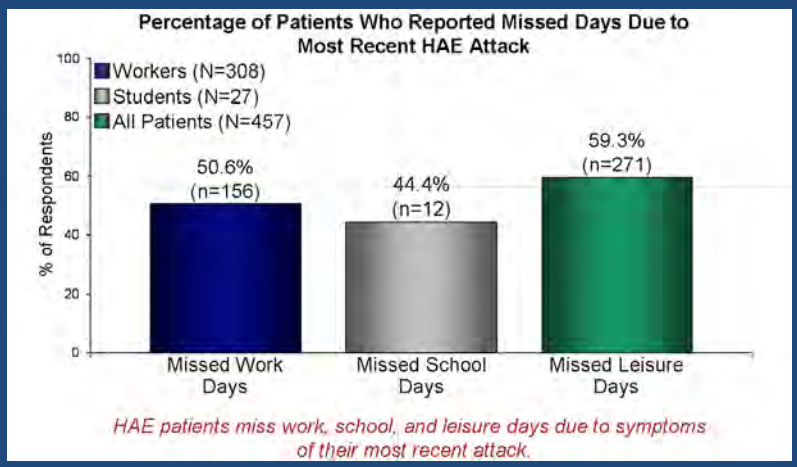
Oropharyngeal and Laryngeal Attacks

Laryngeal Attacks

- Require emergency visits or hospitalization
- May require intervention to prevent airway closure
- Life-threatening
- 50% of patients with HAE will suffer at least one laryngeal attack in their lifetime

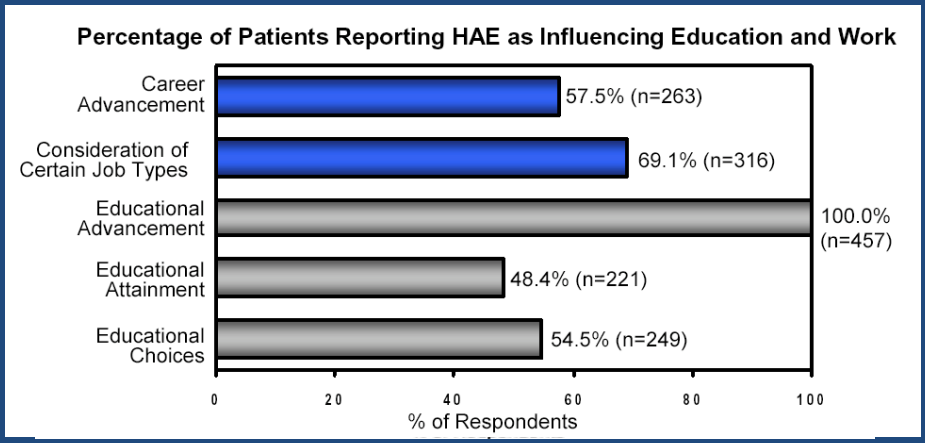
Agostoni A, Cicardi M. *Medicine*. 1992;71:206-215.
Bork K, et al. *Mayo Clinic Proc*. 2000;75:349-354.

Hereditary Angioedema Burden of Illness: Days Lost



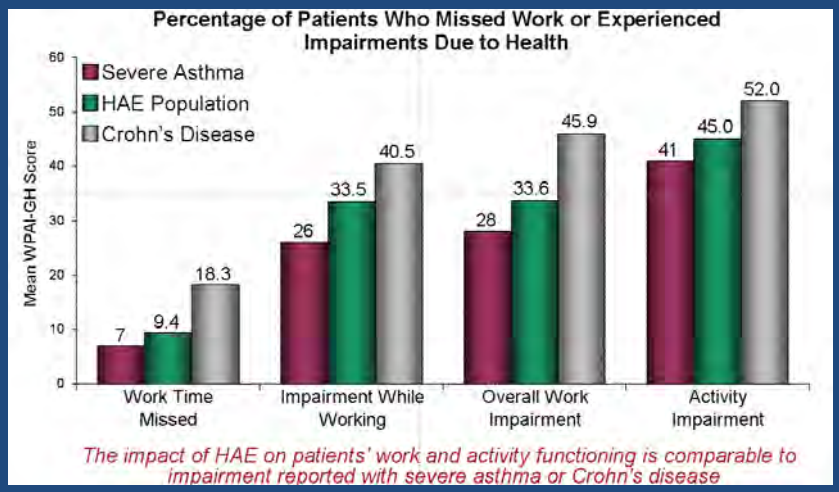
Lumry WR, Castaldo AJ et al. *Allergy Asthma Proc*. 2010 Sep;31(5):407-14.

Hereditary Angioedema Burden of Illness: Education



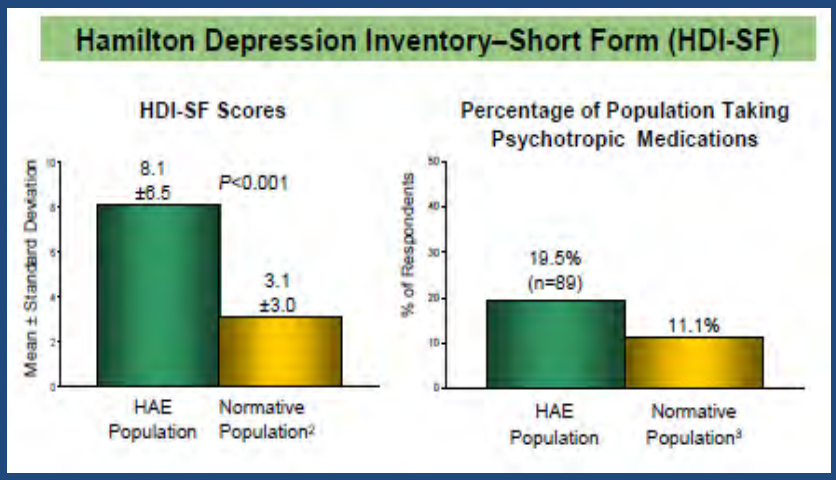
Lumry WR, Castaldo AJ et al. *Allergy Asthma Proc*. 2010 Sep;31(5):407-14.

HAE: Burden of Illness



Lumry WR, et al. *Allergy Asthma Proc*. 2010;31:407-414.

Psychological Impact of HAE



Lumry W, et al. Allergy Asthma Proc. 2010.

HAE Therapy: The Future is Now

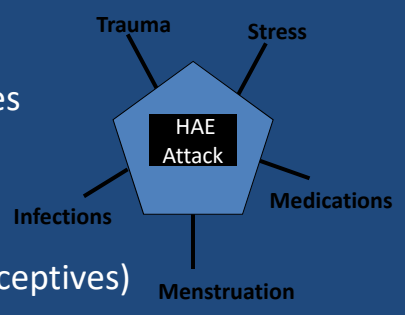
Every Patient Needs an HAE Treatment Plan

Treatment of Hereditary Angioedema

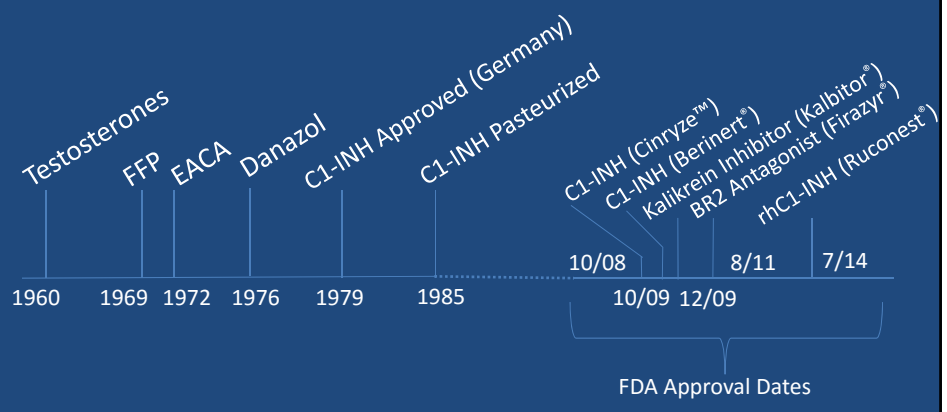
- Conceptually divided into two approaches
  - Treatment of acute attacks
    - Terminate ongoing attack
    - Prevent disability and mortality
  - Prophylactic therapy
    - May be short-term or long-term
    - Minimize attack frequency and severity
    - Prevent hospitalizations and emergency room visits

Triggers of HAE Attacks

- Attacks often unpredictable; 40% of individuals with HAE can identify the cause of an episode
  - Physical trauma
  - Surgical/Medical procedures
  - Infection
  - Emotional stress
  - Some medications (ACE inhibitors, oral contraceptives)
- Hormonal influence
  - Estrogens increase attack severity/frequency

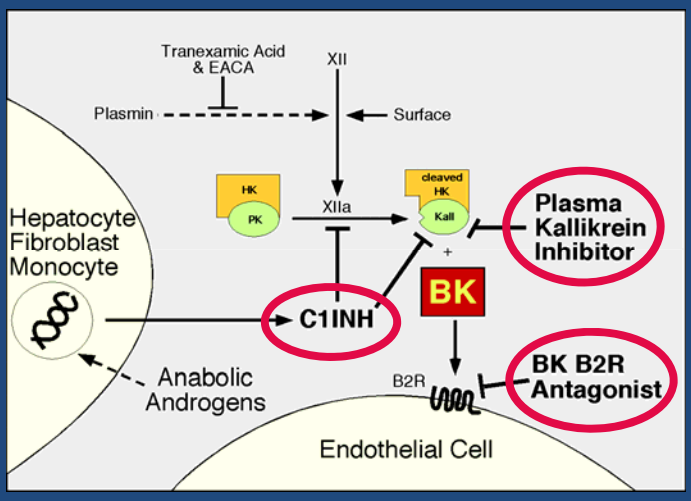


HAE Therapy Timeline



Ann Allerg y Asthma Immunol 2008;100(Suppl2):S2-6 & S23-29; www.fda.gov

Modern Therapies for Hereditary Angioedema (HAE)



B2R=B_2-receptor; BK=bradykinin; EACA=epsilon-aminocaproic acid; HK=high-molecular-weight kininogen; PK=prekallikrein.
Zuraw BL. *Immunol Allergy Clin North Am*. 2006;26:691-708.

Comparison of Acute HAE Therapies

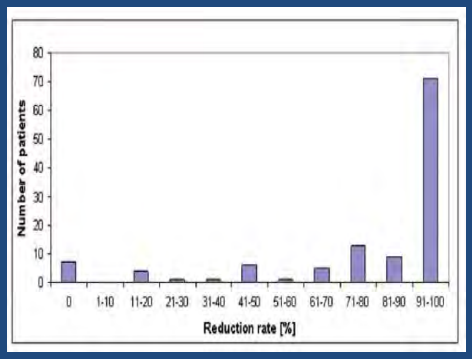
Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Needs IV access • Dependent on plasma supply	• Extensive clinical experience • Relatively long half-life	• **Berinert®:** Approved in USA and many countries worldwide for HAE acute treatment[1] • **Cinryze®:** Approved in USA for HAE long-term prophylactic therapy; in Europe for acute and prophylactic treatment[2,3]
Recombinant C1-INH	• Potential hypersensitivity	• Needs IV access	• No human virus risk • Scalable supply	• **Rhucin®/Ruconest®:** Approved in Europe and USA for HAE acute treatment
Ecallantide	• Allergic reactions • Antibody formation	• Requires administration by a healthcare provider	• No infectious risk • Subcutaneous administration	• **Kalbitor®:** Approved in the USA for acute HAE therapy[5]; currently not approved in Europe
Icatibant	• Local injection reactions		• No infectious risk • Stable at room temperature • Subcutaneous administration	• **Firazyr®:** Approved in USA and numerous other countries for acute HAE therapy[6]

1. Berinert SPC; 2. CINRYZE USPI; 3. CINRYZE SPC; 4. Ruconest SPC; 5. Kalbitor SPC; 6. Firazyr SPC.

Long-Term Prophylactic Treatment for HAE

- Does the patient require long-term prophylaxis?
  - Not everyone with HAE
  - Need varies by individual
    - Frequency, severity, and type of attacks
    - Availability of care
    - Failure of on-demand therapy
- Modalities
  - Anabolic androgens (attenuated or impeded)
  - C1-INH replacement
  - Antifibrinolytics
  - Progestin
- ****Acute treatment should be available for ALL patients on prophylaxis****

Efficacy of Androgens for Long-Term Prophylaxis in HAE



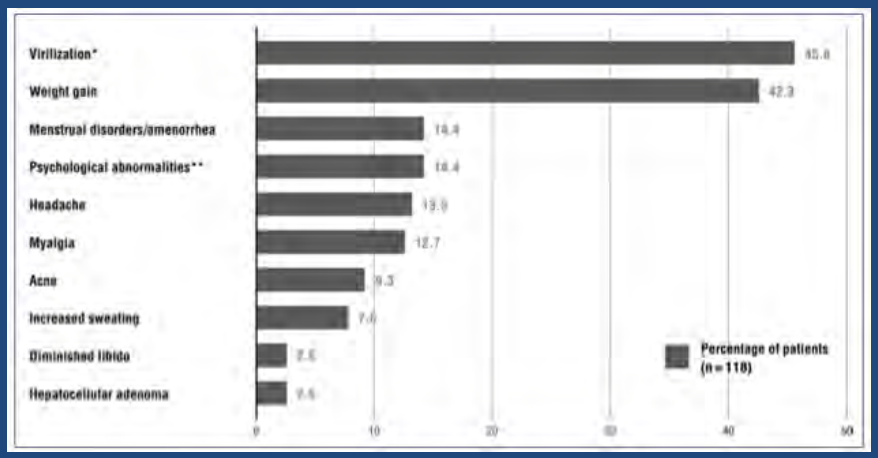
58 of 118 subjects discontinued androgens: 41 due to adverse effects, 7 due to inefficacy

Bork K, et al. *Ann Allergy Asthma Immunol.* 2008;100:153-161

Contraindications to Androgens

- Pregnancy
- Lactating women
- Hepatic disease (viral hepatitis, etc.)
- Children
- CA (prostate / breast)
- Nephrotic syndrome

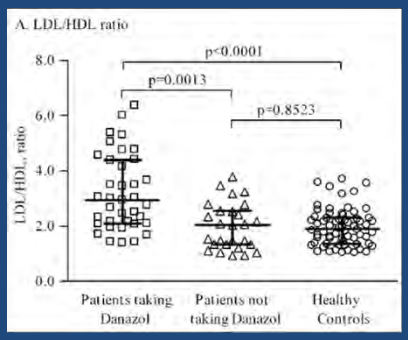
Reported Androgen Side Effects in 118 Patients



Maurer et al. JDDG 2011; 9:99-107
Bork K, et al. *Ann Allergy Asthma Immunol*. 2008;100:153-161

Side Effects of Anabolic Androgens

Virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, altered mood, altered libido



From Széplaki G, et al. *J Allergy Clin Immunol*. 2005;115:864-869.

Bork K, Schneiders V. *J Hepatol*. 2002;36:707-709

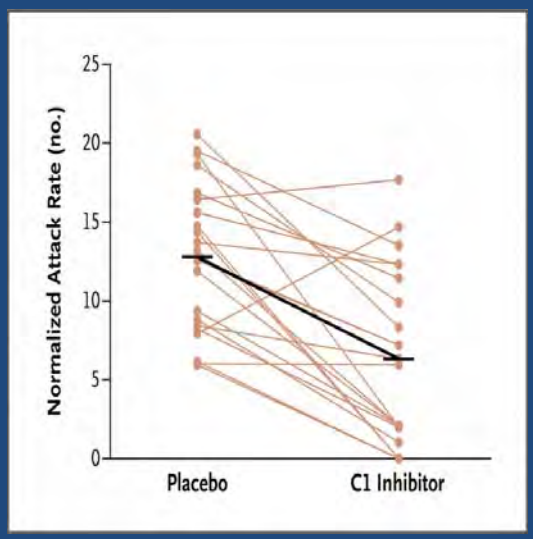
Monitoring with Androgen Therapy

- At treatment initiation and every 6 months:
  - Blood count
  - Liver enzyme values
  - Lipid profile
  - Urine status
  - Ultrasound of the liver for danazol dosages exceeding 200 mg daily and in prepubescent patients (once a year if ≤ 200 mg daily)

Bowen, et al. Ann Allergy Asthma Immunol 2008; 100: S30-S40.

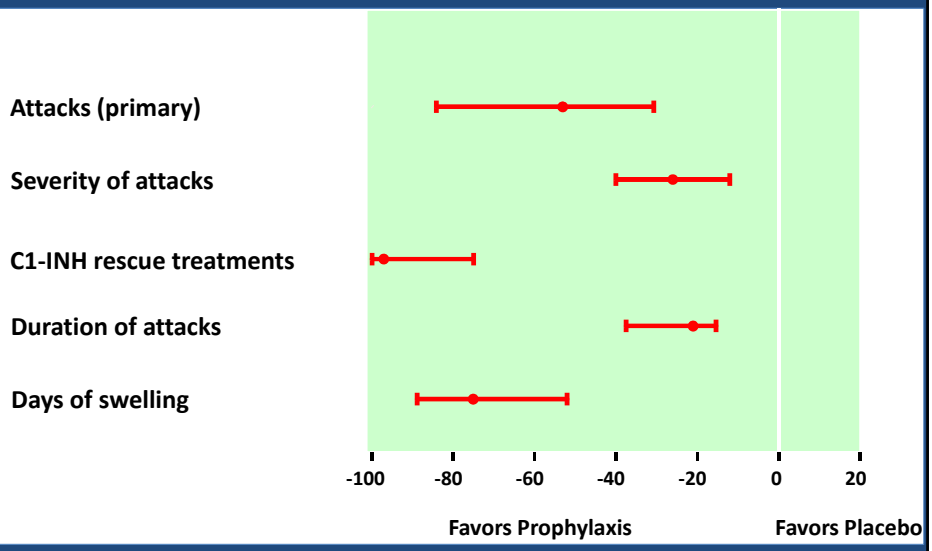
C1-IHN Prophylaxis Associated With Lower HAE Attack Rates

- 3 mo crossover comparing C1INH q 3-4 days vs placebo q 3-4 days
- Average normalized attack rate
  - 12.73 vs 6.26, placebo vs C1-INH
- Average difference in attack rates
  - 6.47 (P<0.001)



Zuraw B, et al. *N Engl J Med.* 2010;363:513-522

Efficacy of Prophylactic Plasma-derived C1-INH Concentrate



US Food and Drug Administration. Available at: www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm094092.pdf..

C1INH Prophylaxis – Side Effects

Table 3 Adverse Reactions in the Open-Label Follow-On Trial

Adverse Reaction	Number (%) of Subjects (N=146) with Adverse Reaction	Number (%) of Infusion Days (N=11,435) with Adverse Reaction
Headache	28 (19)	62 (0.5)
Nausea	26 (18)	29 (0.3)
Rash	15 (10)	30 (0.3)
Vomiting	15 (10)	17 (0.1)
Pyrexia	7 (5)	7 (<0.1)
Catheter Site Pain	4 (3)	5 (<0.1)
Dizziness	3 (2)	4 (<0.1)
Erythema	3 (2)	3 (<0.1)
Pruritus	3 (2)	4 (<0.1)

Zuraw B, et al. *N Engl J Med.* 2010;363:513-522
Cinryze PI, Accessed 2014

C1-INH and Thrombosis

- Physician Survey – Kalaria et al.
- 66 physicians
  - 856 HAE patients treated with C1INH
  - 5 patients with reported thromboembolic events (0.6%)
  - Of 17 patients with indwelling catheters, 3 with thromboembolic events (18%)

Kalaria S. Allergy Asthma Proc. 2013

Comparison of Prophylactic Therapies: Attenuated Androgens and C1-INH

	Attenuated Androgens[1]	C1-INH[2]
Advantages	Low cost Oral administration	Replaces missing (Type I HAE) or abnormally functioning (Type II HAE) C1-INH
Disadvantages	Adverse effects	Intravenous access High cost
Potential side effects	Weight gain Liver damage Hyperlipidemia Hepatocellular carcinoma Mood changes	Potential for blood-borne pathogens Port thrombosis and infection
Contraindicated populations	Pregnant women Children	Hypersensitivity to blood products

1. Danzol SPC; 2. CINRYZE SPC.

Guidance on Treatments for HAE

- Consensus Statements/ Working Groups
  - Hereditary Angioedema International Working Group (HAWK): Evidence-based treatment consensus publication; Cicardi et al.
  - WAO Guideline for the Management of Hereditary Angioedema; Craig et al.
  - International Consensus on Hereditary and Acquired Angioedema; Lang et al.
  - US Hereditary Angioedema Association Medical Advisory Board Consensus Document; Zuraw et al.
  - Canadian Hereditary Angioedema Guideline; Betschel et al.

Cicardi M, et al. Allergy. 2012 Feb;67(2):147-57.
Craig, et al. World Allergy Organ J. 2012 Dec;5(12):182-199
Lang, et al. Ann Allergy Asthma Immunol. 2012 Dec;109(6):395-402
Zuraw, et al. J Allergy Clin Immunol: In Practice 2013;1:458–467
Betschel, et al. Allergy Asthma Clin Immunol. 2014 Oct 24;10(1):50

HAE Guidelines: Areas of Agreement

- On-demand treatment necessary for every HAE patient
  - Must be reliably and efficiently accessible
  - Includes patients receiving long-term prophylaxis
- All or nearly all attacks eligible for treatment
- Laryngeal attacks uniquely life-threatening and require special attention
- Early treatment of attacks beneficial in reducing morbidity and complications
- Prophylactic therapy indicated for patients in whom on-demand treatment alone is unsatisfactory

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1. Bowen T, et al. Allergy Asthma Clin Immunol 2010;6:24; 2. Cicardi M, et al. Allergy 2012;67:147–57; 3. Craig T, et al. World Allergy Organ J 2012;5:182–199; 4. Lang, et al. Ann Allergy Asthma Immunol 2012;109:395–402; 5. Zuraw, et al. J Allergy Clin Immunol: In Practice 2013;1:458–467

HAE Guidelines: Areas Lacking Clarity

- Specific indications for prophylaxis
- "Preferred" agents for prophylactic or acute HAE treatment
  - Exception is special populations: pediatrics, pregnancy

1. Bowen T, et al. Allergy Asthma Clin Immunol 2010;6:24; 2. Cicardi M, et al. Allergy 2012;67:147–57; 3. Craig T, et al. World Allergy Organ J 2012;5:182–199; 4. Lang, et al. Ann Allergy Asthma Immunol 2012;109:395–402; 5. Zuraw, et al. J Allergy Clin Immunol: In Practice 2013;1:458–467

Acute Treatment Plan

- Essential for every person/family with HAE
- Tailored to individual circumstances
- Rapidly and efficiently accessible
- Choices
  - Medication
  - Administration location(s)
  - Self-administration
- Develop a "back-up" plan
- Be equipped to navigate the health care system

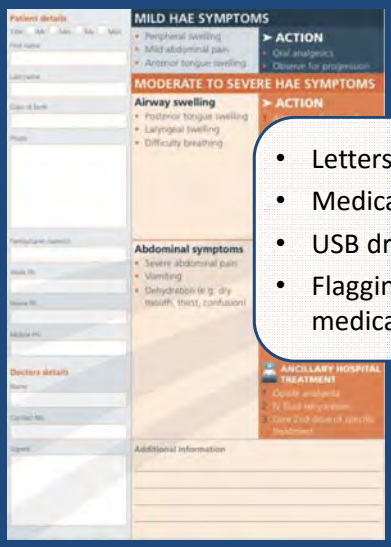
Riedl MA. Immunol Allergy Clin N Am 2013;33:471–485

Acute Treatment Plan Logistics

- Reliable, accessible and efficient
- Self-administration
  - Intravenous infusions
  - Subcutaneous injections
  - Personal comfort level
  - Education/technical instruction
  - Family or friend assistance
  - Medication labeling
- Home health nursing "on call"
- Hospital-based acute care
  - "Brown-bagging" medication

- What works best for the patient?
- Is the plan reliable?

Hereditary Angioedema Action Plan



- Letters
- Medical ID bracelets
- USB drives
- Flagging the electronic medical record

Date

To Whom It May Concern:

Ms./Mr. _____ has been diagnosed with Hereditary Angioedema (HAE) and is under my care to treat her/his condition. This genetic condition leads to sporadic episodes of cutaneous, intestinal, and/or [illegible] that may be severely disabling and life-[illegible]

[illegible]E attacks requires one of the following [illegible]red as quickly as possible to abort

[illegible]0-2000 units intravenously
[illegible]) 30 mg subcutaneously
[illegible] mg subcutaneously

[illegible]dications may be necessary in the event [illegible]urring angioedema symptoms.

[illegible]n, management of acute attacks may [illegible] airway monitoring, analgesic and [illegible]intravenous fluids as appropriate. **[illegible]Costeroids are not effective in treating [illegible]d form of angioedema.** Epinephrine may [illegible]ing measure for significant laryngeal edema, however airway compromise requires immediate dosing of the effective medications listed above and careful monitoring.

It is medically necessary that the patient carry the listed HAE medications and related treatment supplies while traveling.

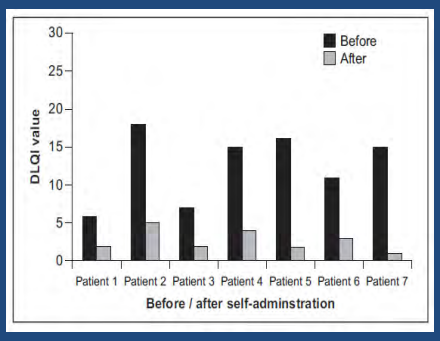
I may be reached with any questions regarding this condition at XXX-XXX-XXXX.

Sincerely,

Courtesy of Dr Connie Katelaris

Home Administration of HAE Therapy

- Demonstrated benefits with proper implementation:
  - Increased QoL, flexibility & convenience
  - Decreased time to treatment, severity / duration of attacks
- Considerations:
  - Individual patient
  - Route of administration
  - Training programs
  - Counseling / consent



Bygum. Eur J Dermatol 2009

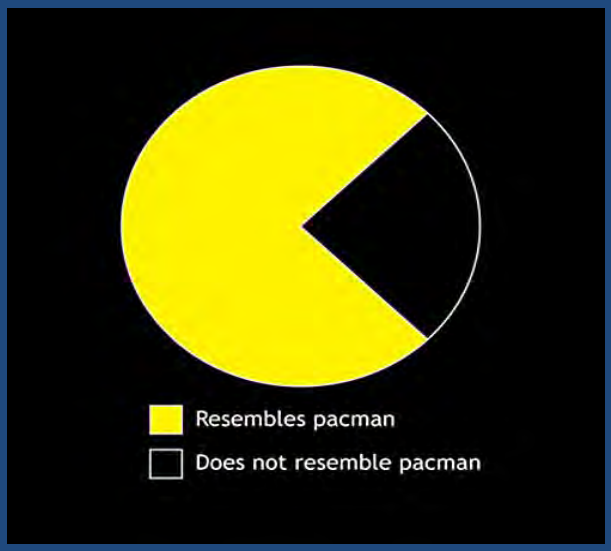
Longhurst H, et al. *Allergy Asthma Clin Immunol*. 2010;6(1):22.
Levi M, et al. *J Allergy Clin Immunol*. 2007;117:904-908.
Dagen C, et al. *Allergy Asthma Clin Immunol.* 2010;6(1):11.
Bygum A, et al. *Eur J Dermatol*. 2009;19(2):147-151.
Kreuz W, et al. *Transfusion*. 2009; 49(9);1987-1995.

Routine Prophylaxis vs. Acute Treatment Alone

- Consider:
  - Nature of HAE symptoms
    - Frequency
    - Severity
    - Rapidity of onset and progression
    - Anatomical location
    - Level of functional impairment
    - Degree of psychological impact
  - Availability of a rapid, efficient acute treatment plan
  - Impact of HAE on work or school
  - Restoring 'normalcy' to daily life

1. Craig T, et al. World Allergy Organ J 2012;5:182–199; 2. Cicardi M, et al. Allergy 2012;67:147–157

The Science and the Art of Medicine



Individualization of HAE Therapy

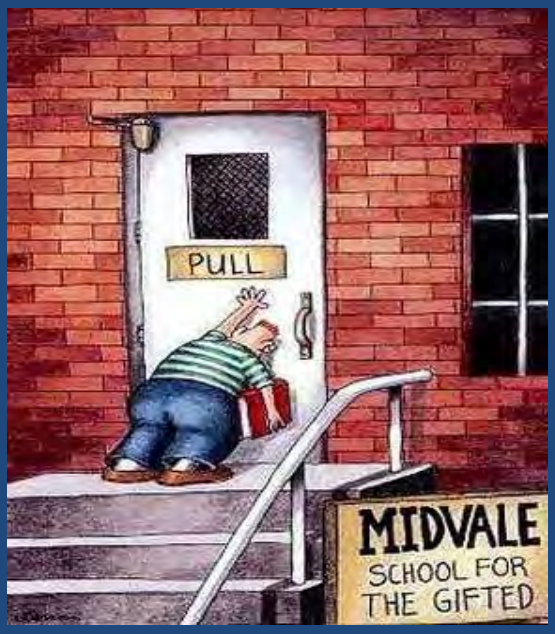
- Patient factors
  - Attack frequency
  - Rapidity of progression
  - Laryngeal attacks
  - Access to medical care
  - History of frequent hospitalization
  - Treatment complications
- Medication factors
  - Efficacy
  - Safety
  - Administration route
  - Patient preference/ tolerability
  - Administration location
  - Source
  - Cost

The Comprehensive Treatment Plan: Essentials of Modern HAE Therapy

- Components of the Medical Management Plan
  - Acute Treatment Plan for Every Person with HAE
  - Routine Prophylaxis for Some
  - Logistics of Treatment Plan
  - Monitoring for Efficacy and Side Effects

Monitoring for Efficacy and Side Effects

- Known and unknown risks of medications
  - Androgens
  - Plasma products
  - Local and systemic treatment reactions
  - IV access issues
- Individual patient variability in response to therapies
- HAE is a complex, highly-variable, chronic condition
  - benefits of periodic monitoring



Incorporating New Treatments for HAE

- Treatment in the U.S. circa 2010
  - 74% of treated HAE attacks seen in ED/hospital

According to MDs:
22% of patients dissatisfied with treatment
65% of patients somewhat satisfied with treatment
13% of patients very satisfied with treatment

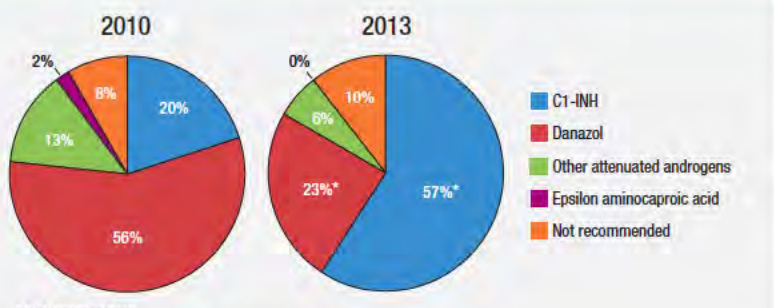
20-30% MDs not familiar with C1INH products
40-50% MDs not familiar with ecallantide or icatibant

Percentage of MDs using specific therapy to treat HAE attacks (N= 172)

Riedl et al. Ann Allergy Asthma Immunol. 2011

Prescribed Long-Term Prophylactic Therapies in U.S. 2010 vs. 2013

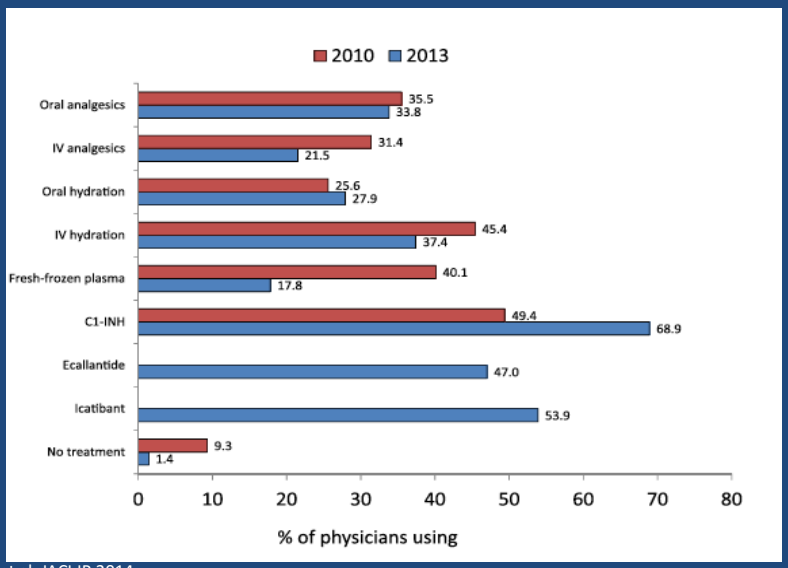
Figure 2. Long-term HAE prophylaxis, medications reported as used most frequently, 2010 vs 2013. Data represent percentage of physicians reporting.



* P<0.00005 vs 2010
Note: "Other attenuated androgens" includes stanozolol and oxandrolone

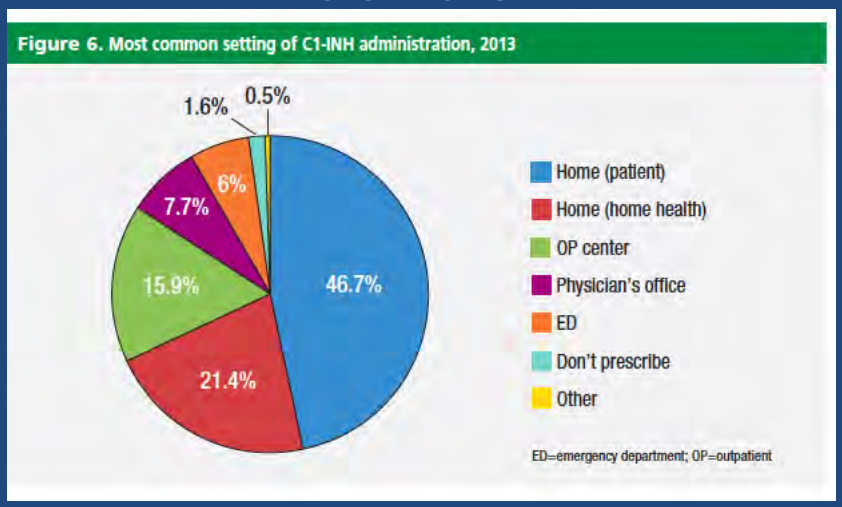
Riedl M, et al. JACI:IP 2014.

Prescribed Acute HAE Therapies in U.S. 2010 vs. 2013



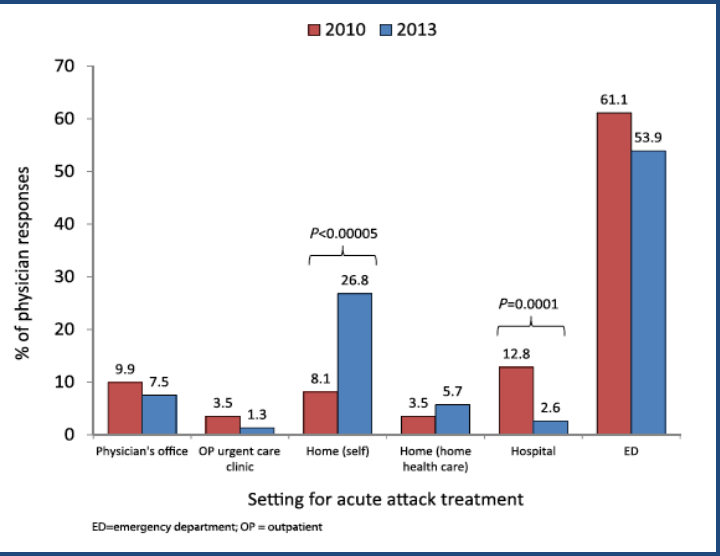
Riedl M, et al. JACI:IP 2014.

Location of C1INH Administration in U.S. 2013



Riedl M, et al. JACI:IP 2014.

Location of HAE Attack Treatment in U.S. 2010 vs 2013



Riedl M, et al. JACI:IP 2014.

Current state of hereditary angioedema management: A patient survey

Aleena Banerji, M.D.,[1] Paula Busse, M.D.,[2] Sandra C. Christiansen, M.D.,[3,4] Henry Li, M.D.,[5] William Lumry, M.D.,[6] Mark Davis-Lorton, M.D.,[7] Jonathan A. Bernstein, M.D.,[8] Michael Frank, M.D.,[9] Anthony Castaldo,[10] Janet F. Long,[10] Bruce L. Zuraw, M.D.,[3,11] and Marc Riedl, M.D., MS[3,11]

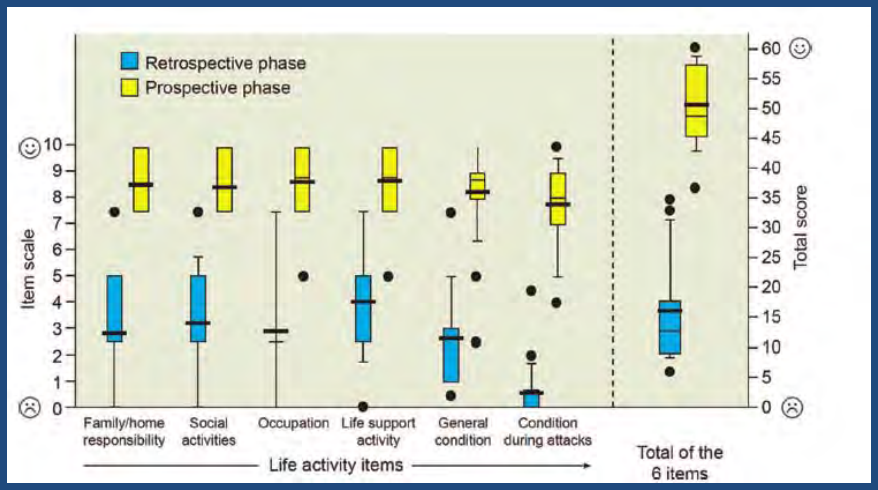
Allergy Asthma Proc 36:213–217, 2015

Before and after, the impact of available on-demand treatment for HAE

Authors: Christiansen, Sandra C.; Bygum, Anette; Banerji, Aleena; Busse, Paula; Li, Henry; Lumry, William; Davis-Lorton, Mark; Bernstein, Jonathan A.; Frank, Michael M.; Castaldo, Anthony; Long, Janet F.; Riedl, Marc; Zuraw, Bruce L.

Source: Allergy and Asthma Proceedings, Volume 36, Number 2, March/April 2015, pp. 145-150(6)

Improvements in Quality of Life with C1INH IRT



Kreuz et al. Transfusion 2009;49:1987-1995

C1INH Therapy: Patient Self-Administration

On demand treatment and home therapy of hereditary angioedema in Germany - the Frankfurt experience

Emel Aygören-Pürsün*, Inmaculada Martinez-Saguer, Eva Rusicke, Thomas Klingebiel, Wolfhart Kreuz

HAE international home therapy consensus document

Hilary J Longhurst[1*], Henriette Farkas[2], Timothy Craig[3], Emel Aygören-Pürsün[4], Claire Bethune[5], Janne Bjorkander[6], Konrad Bork[7], Laurence Bouillet[8], Henrik Boysen[9], Anette Bygum[10], Teresa Caballero[11], Marco Cicardi[12], John Dempster[13], Mark Gompels[14], Jimmy Gooi[15], Sofia Grigoriadou[16], Ursula Huffer[17], Wolfhart Kreuz[18], Marcel M Levi[19], Janet Long[20], Inmaculada Martinez-Saguer[21], Michel Raguet[22], Avner Reshef[23], Tom Bowen[24], Bruce Zuraw[25]

Challenges in Practice with the Treatment of Acute Attacks of HAE

- Not understanding risks associated with acute attacks (in particular laryngeal attacks)
- Not having treatment for an acute attack available
  - Hospital
  - At home
- Not knowing when to treat
- Lacking training on self-administration
- Costs of medication/administration
  - Local reimbursement policies

Dagen C,et al. *Allergy Asthma Clin Immunol.* 2010;6(1):11.

"Uh-oh, your coverage doesn't seem to include illness."

"The only thing constant is change"

- Heraclitus of Ephesus (500 BC)

Addressing Education and Knowledge Gaps for Rare Conditions

- HAE: Estimated prevalence of 1:50,000
- Increasing Awareness in the Medical Community
  - Physician/HCP education programs
  - Specialists, generalists, hospitals/clinics
  - Medical School/ Residency training programs
  - Medical publications
- Patient/Family education programs
  - Awareness of symptoms, complications
  - Importance of Family testing
  - Knowledge of treatment options
- **HAEi and HAEA Efforts**
- **Industry Efforts**
- **Data collection on knowledge and clinical care in health care systems globally**

Unknowns in HAE Pathophysiology

- What specifically...
  - Starts
  - Propagates
  - Ends

  ...episodes of hereditary angioedema
- Factors causing variability in clinical symptoms/course
  - Mediator-receptor variations
  - Kinin degradation variability
  - Genetic polymorphisms
  - Epigenetics
- Can we develop tests with prognostic value in HAE?
  - Diagnostic value in other forms of angioedema

HAE Patient Registry and Biorepository

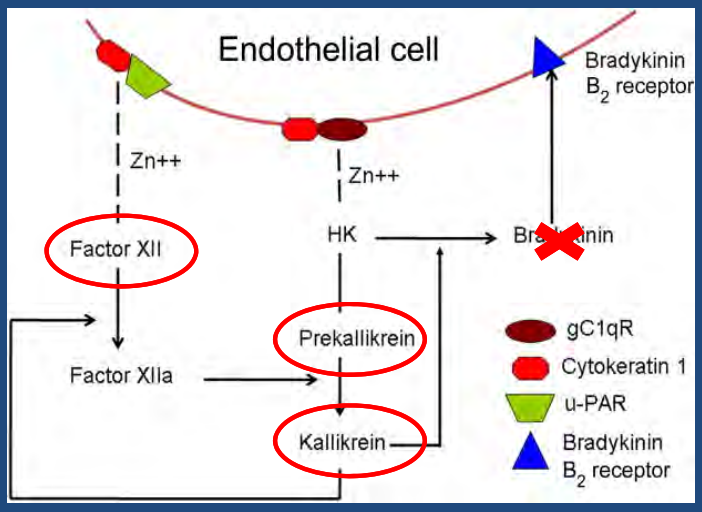
HAE Modifier Genes

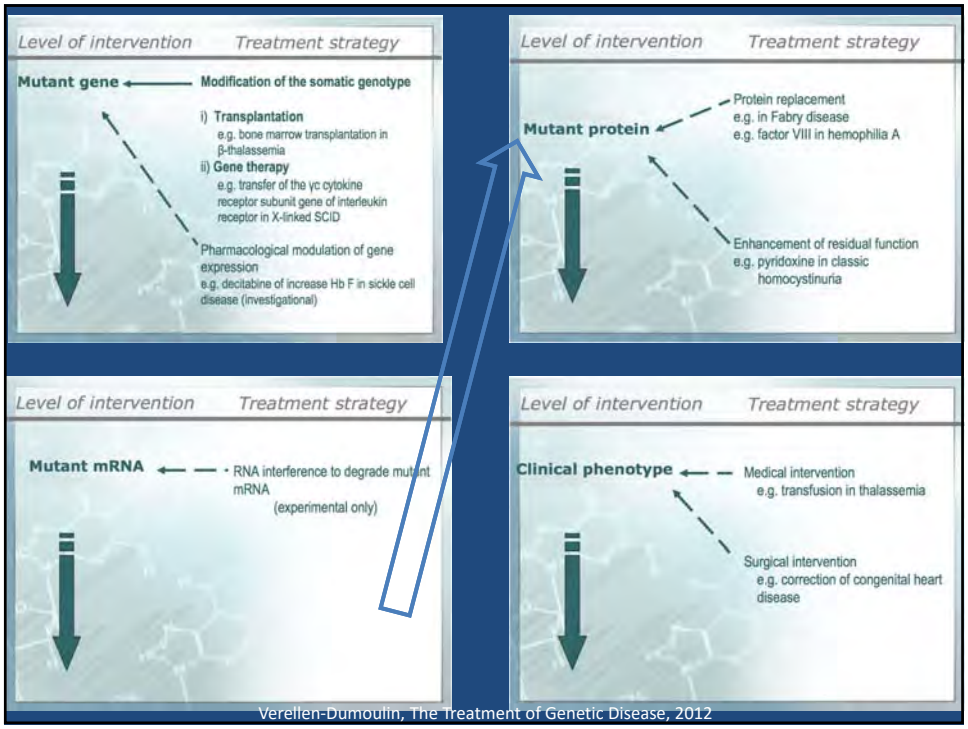
- López-Lera A, et al. Disease-modifying factors in hereditary angioedema: an RNA expression-based screening. Orphanet J Rare Dis. 2013 May 20;8:77.

Results: Instead of a single, common disease-associated expression pattern, we found different transcriptome signatures in two of the families studied. In one of them (referred to as DR family), symptoms correlate with the upregulation of 35 genes associated to the biological response to viral infections (including RSADs, OAS, MX and ISG pathway members) and immune response. In another pedigree (Q family), disease manifestation is linked to the upregulation of 43 genes with diverse functions, including transcription and protein folding. Moreover, symptoms-free members of the Q pedigree display relatively higher expression of 394 genes with a wide diversity of functions.

Looking Ahead: Prophylactic HAE Therapy

- PHASE 3
  - Subcutaneous C1-INH Concentrate
  - Monoclonal Antibody against kallikrein
- Earlier Phase Development
  - Oral Kallikrein Inhibitors
  - Monoclonal Antibody against Factor XII
  - RNAi-based treatment
    - Prekallikrein
    - Factor XII
  - Gene Therapy





Verellen-Dumoulin, The Treatment of Genetic Disease, 2012

HAE in the Future

- Rapid treatment for every patient early in attack
- Convenient medication dosing
- Optimized and improved prophylaxis

CLINICAL CARE

- Understanding of disease variability (genetics, mediators, triggers): **Scientific registries**
- **Studies** to demonstrate to optimal treatment strategies for improved clinical outcomes and cost-effectiveness

RESEARCH

- Centers to offer comprehensive **education**, evaluation, development of management plans, and support programs

EDUCATION


Thank You