

# Hereditary Angioedema

Creating Awareness and Improving Patient Outcomes

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# Hereditary Angioedema Overview (HAE)

- Background and Epidemiology
- Pathophysiology
- Clinical Presentation
- Diagnostic Evaluation
- Treatment



# What is Hereditary Angioedema?

- Debilitating and potentially life-threatening autosomal dominant disease
  - Caused by an inherited deficiency in C1 esterase inhibitor (C1 INH)
  - Characterized by attacks of cutaneous or mucosal edema that may cause discomfort or pain
    - Includes extremities, face, GI tract, larynx, trunk, urogenital
    - If untreated, 30%-56% mortality rate from asphyxiation
- 1500's – Donati described case of angioedema without urticaria
- 1888 – Hereditary component proposed by Sir William Osler
- 1963 – C1 INH defect in HAE described by Drs. Donaldson and Evans



# HAE Epidemiology

- Autosomal dominant hereditary pattern
  - 25% of those diagnosed have a spontaneous gene mutation
- No predilection for race, gender, age
- Reliable data on incidence is lacking
- Worldwide incidence thought to be 1:10,000 to 1:50,000
  - US population: approximately 6,000 affected



# Impact: Patients and Healthcare Systems

- Web-based survey of 457 HAE patients found:
  - unable to engage in normal activities for 20 to 100 days per year
  - 1/3 of undiagnosed patients undergo unnecessary surgery
  - 51% missed  $\geq 1$  work day due to most recent attack
  - 44% missed  $\geq 1$  school day due to most recent attack
  - 100% felt disease prevented them from advancing in school
  - 69% felt unable to consider certain jobs
  - 58% affected career advancement
- In a 2007 retrospective study of two large US databases
  - HAE + AE accounted for 35,000 hospital days and hospital costs of \$63 million
  - 45% of HAE patients required hospitalization; 18.3% of AE patients

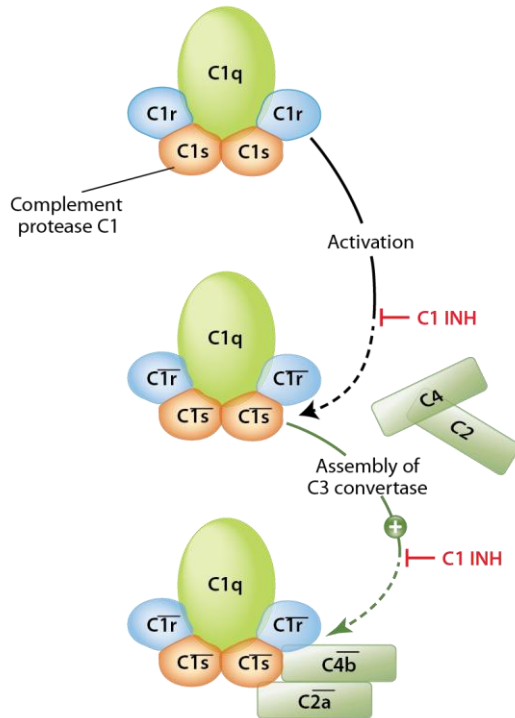


# Pathophysiology

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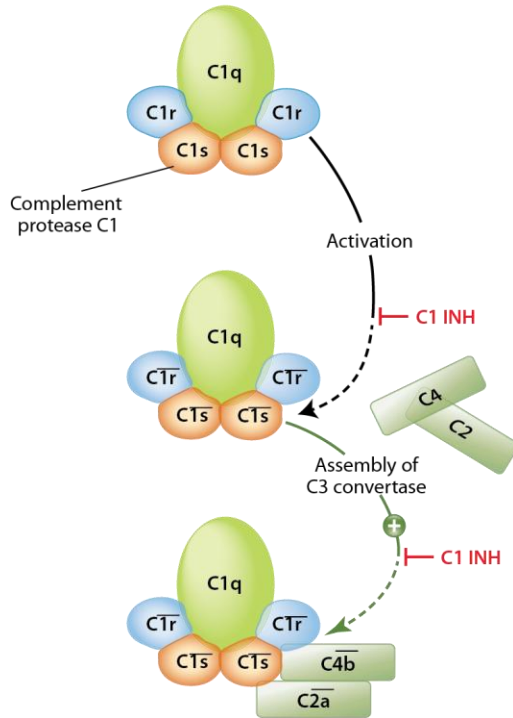
# C1 INH as a Control Protein

## Complement Pathway

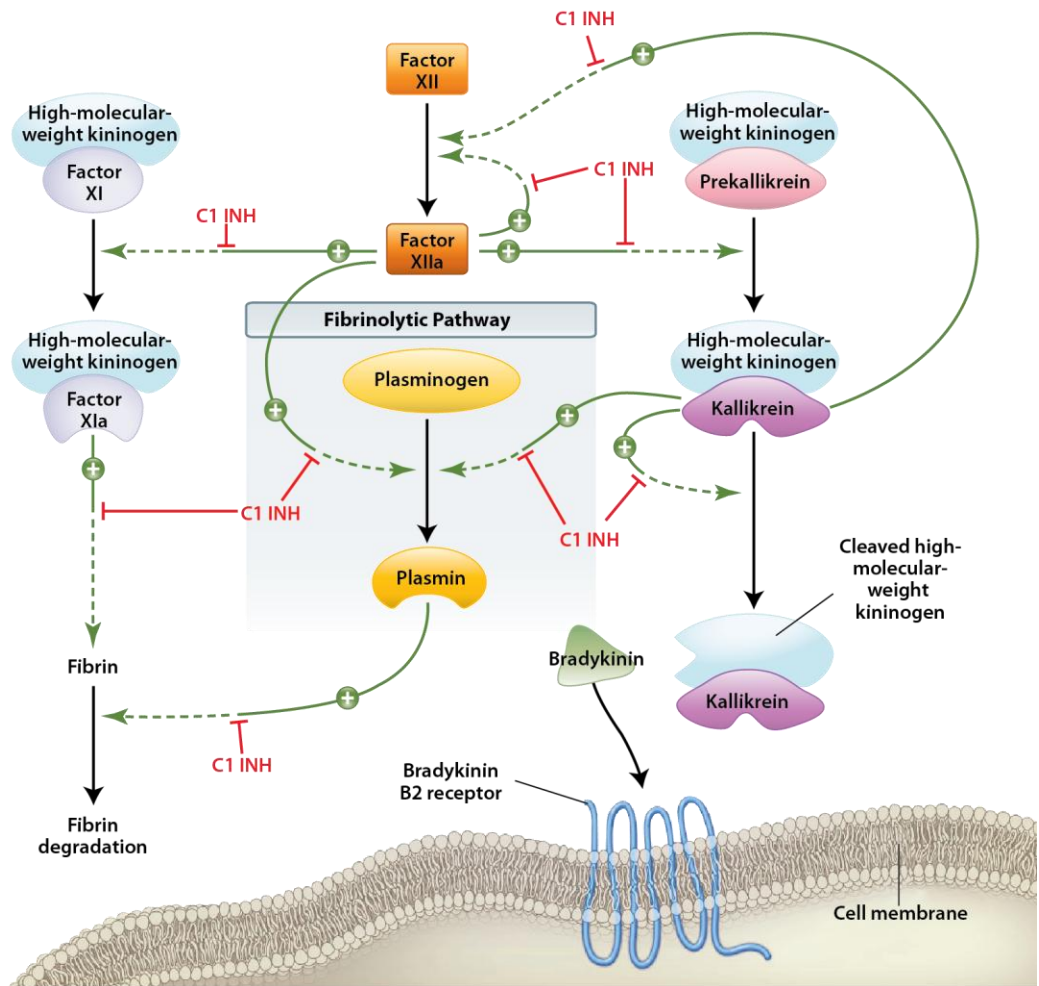


# C1 INH as a Control Protein

## Complement Pathway



## Contact Activation Pathway

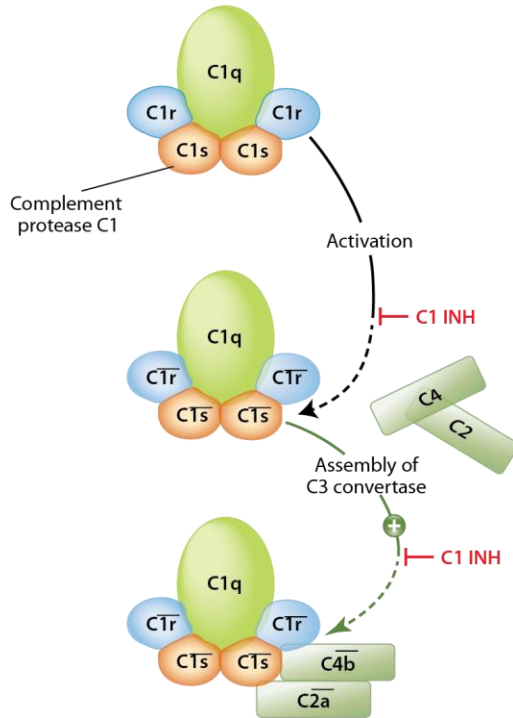


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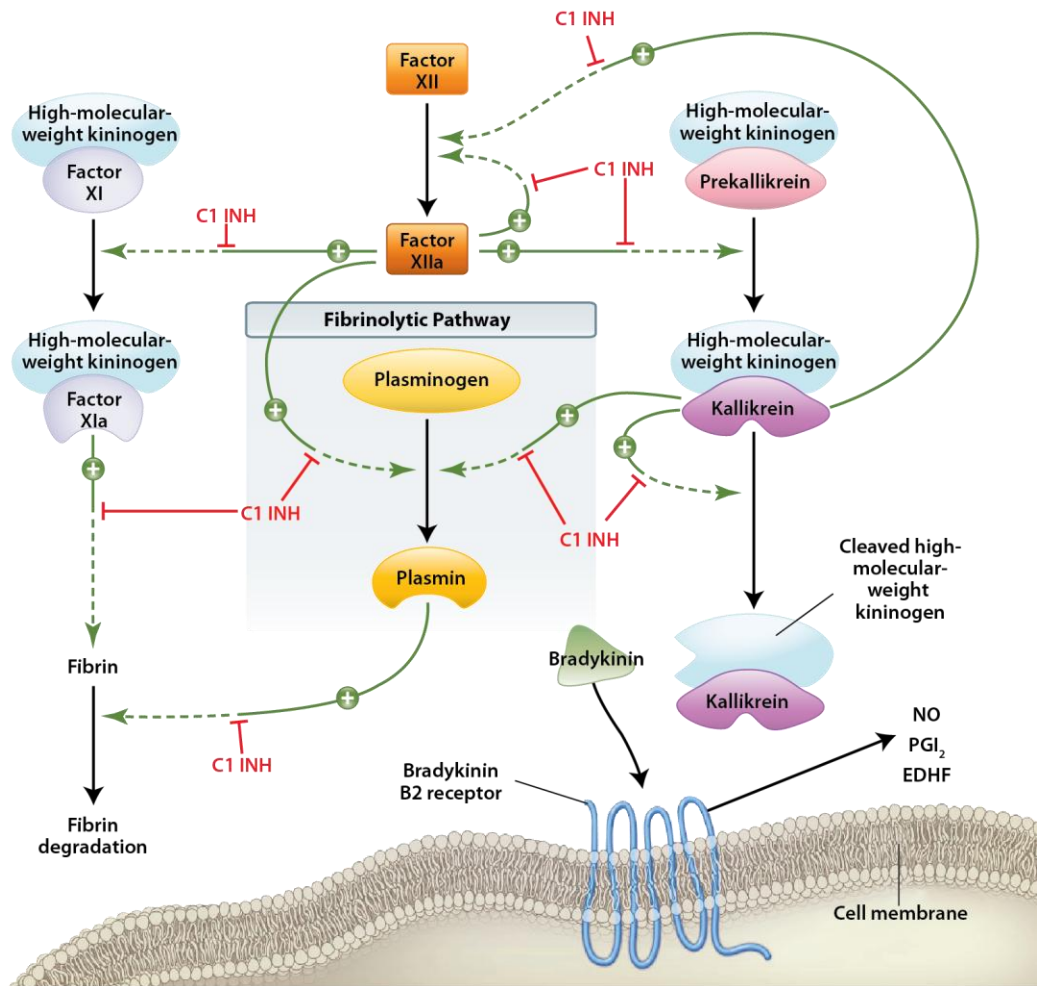


# C1 INH as a Control Protein

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# Clinical Presentation

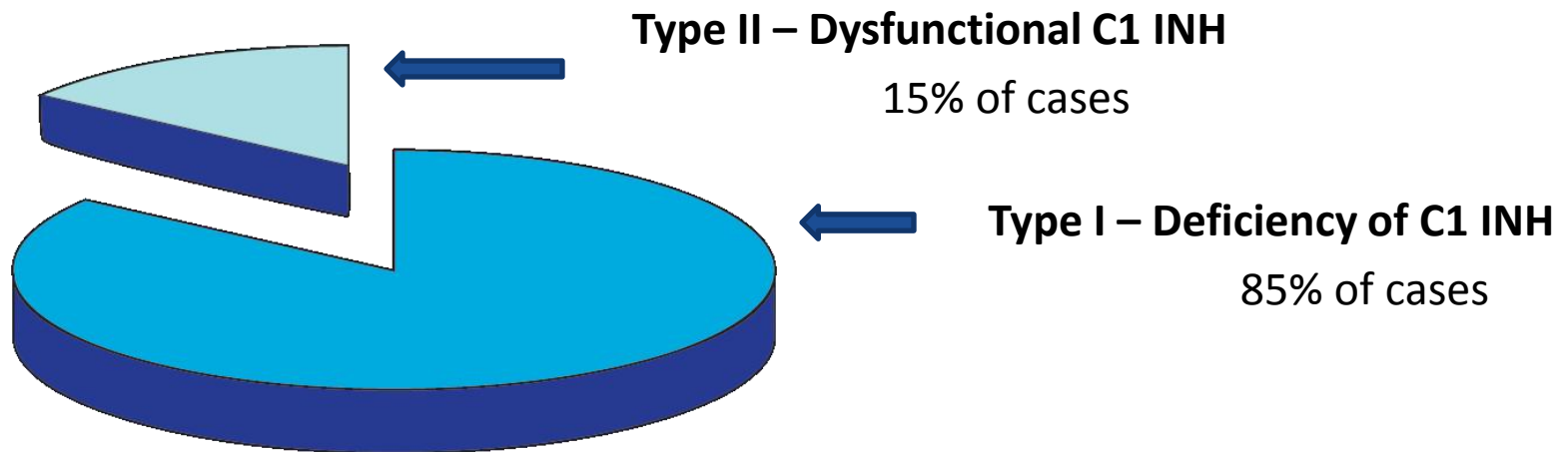
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# Types of Angioedema

- C1 INH mutations

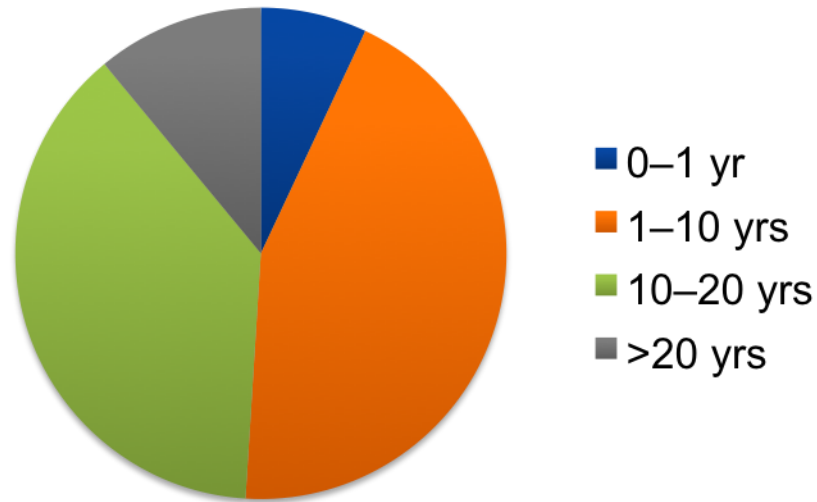
Type I → low circulating C1 INH protein

Type II → dysfunctional C1 INH protein



# Onset of HAE Symptoms

- Mean age of onset: 11.2 yrs
- 51% of patients experienced symptoms by 10 yrs
- Time between first attack and accurate diagnosis: 10 to 22 years



# Clinical Presentation

- Severity of attacks
  - Unrelated to magnitude of C1 INH dysfunction
  - Highly variable in and among patients
  - Clinical manifestations often more severe in women
- Pattern and frequency of attacks
  - Untreated symptomatic patients may have episodes greater than once a week
  - Highly variable in and among patients
- Symptom cycle
  - Worsening symptoms over first 24 to 36 hr
  - Slow resolution during next 36 to 48 hr
  - More severe episodes can last 3 to 5 days



# Triggers of HAE Episodes

- Unpredictable precipitating event
  - Only 40% of patients can identify the cause of an episode
  - Physical trauma
  - Surgical/Medical procedures
    - Dental work
  - Mechanical pressure
    - Typing, writing, sewing, mowing lawn, hammering, long periods of standing
  - Infection
  - Emotional stress
  - Some medications (ACE inhibitors, oral contraceptives)
- Hormonal influence
  - Estrogens increase attack severity/frequency



# Areas Involved in HAE Attacks

- Swelling can occur in any part of the body and often involves multiple sites
- In a study by Bork et al in 2006:

Site	Incidence
Extremity	97.5%
Abdomen	93%
Face	79%
Genital	65%
Laryngeal	52%



# Extremity Attacks: Hand



# Abdominal Attacks

- Occur in 80 - 93% of patients with HAE
- Mild to severe intractable pain
- Vomiting common; constipation/diarrhea may occur
- Symptoms mimic surgical emergencies; 1/3 patients experiencing an abdominal attack will undergo unnecessary surgery
  - Intestinal obstruction
  - Fluid loss may lead to hypovolemic shock
  - Occasionally rebound tenderness and guarding



# Abdominal Imaging

- Abdominal films, ultrasonography, and CT scans may be useful to identify edema of the intestinal wall
- No recommendations but may seem thumb printing

Marked thumb printing  
in simple scout film of  
27yo male with HAE



# Urogenital Attacks

- Embarrassing to patients = under reported
- 65% of patients experience urogenital attacks at some point
- Typical triggers: intercourse, local trauma
- Patient consequences
  - Painful urination
  - Difficult to sit
  - Days lost at school and work



# Laryngeal Attacks

- In untreated patients, 30% - 56% mortality
- 50% of HAE patients will suffer at least one laryngeal attack in their lifetime
- Unpredictable, can occur at any age
- Study of fatal laryngeal attacks (N=6)
  - 9 yr old boy, fatal laryngeal attack was first HAE attack
  - 30 yr old with >100 prior laryngeal attacks
- Duration from symptom onset to asphyxiation
  - Range, 20 min to 14 hrs



# Prior to Attack



# Onset of Attack



# Hospitalization



# Intubation for Laryngeal Extension



Time from prodrome: approximately 8 – 10 hours



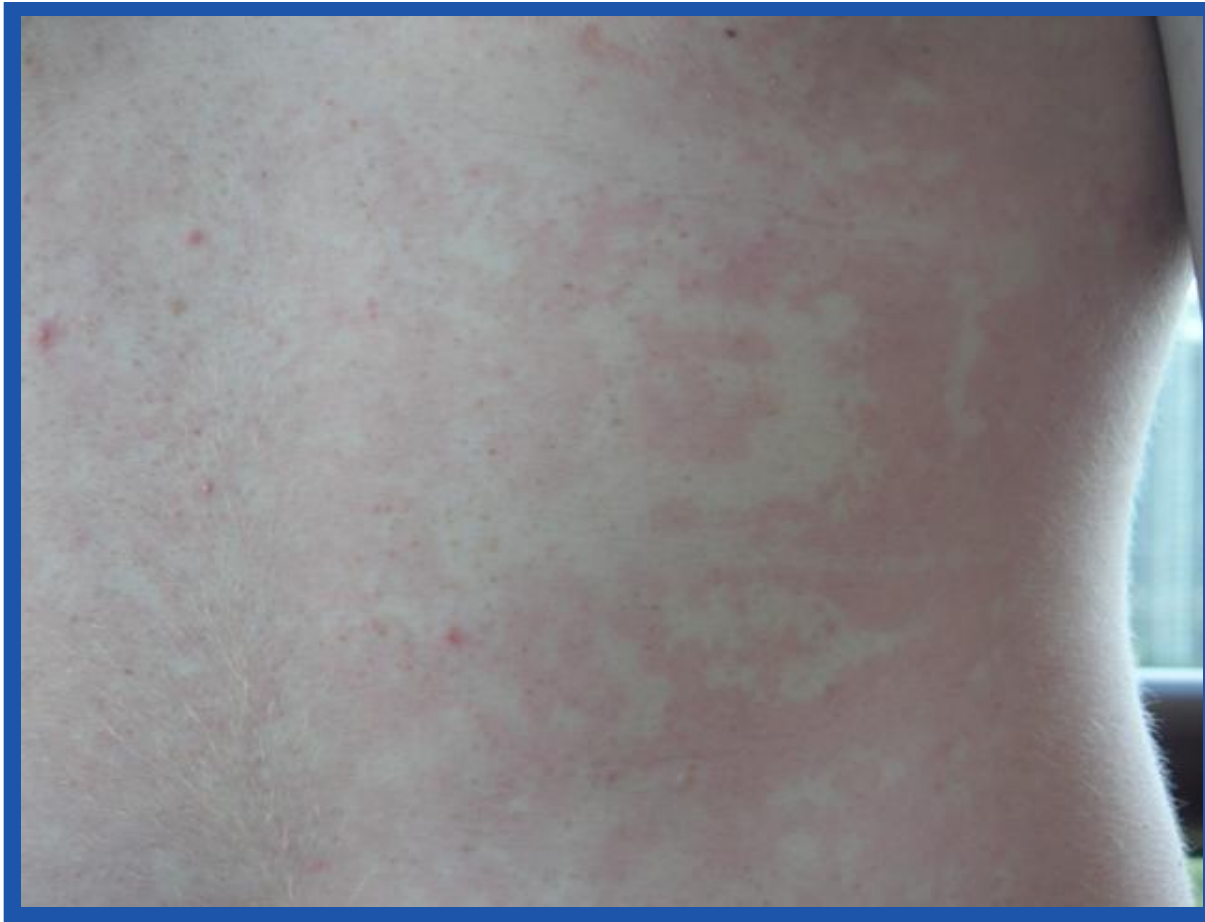
# Clinical Differences

## C1 INH deficiency and allergic angioedema

- Prodrome may precede attack
- Onset may be slower than IgE mediated swelling
- Abdominal involvement is common in HAE
- Nonpruritic subcutaneous or submucosal edema
- No urticaria
- 30% of patients will have erythema marginatum



# Erythema marginatum



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# Diagnostic Evaluation

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# Differential Diagnosis by Mechanism

Allergic IgE-Mediated Mast Cell/Basophil Degranulation	Nonallergic Mast Cell/Basophil Degranulation	Bradykinin Mediated	Leukotriene Mediated	Unclear
Drug allergy	Idiopathic angioedema	HAE	Aspirin/NSAID drug reaction	HAE III
Food allergy	Autoimmune urticaria/angioedema	Acquired angioedema		Gleich's syndrome
Venom hypersensitivity	Radiocontrast media anaphylactoid reaction	ACE inhibitor induced angioedema		Idiopathic angioedema
Latex allergy	Drugs (morphine, polymyxin, d-tubocurarine)			
Aeroallergens (ocular)	Physical urticaria/angioedema			
	Exercise-induced anaphylaxis			



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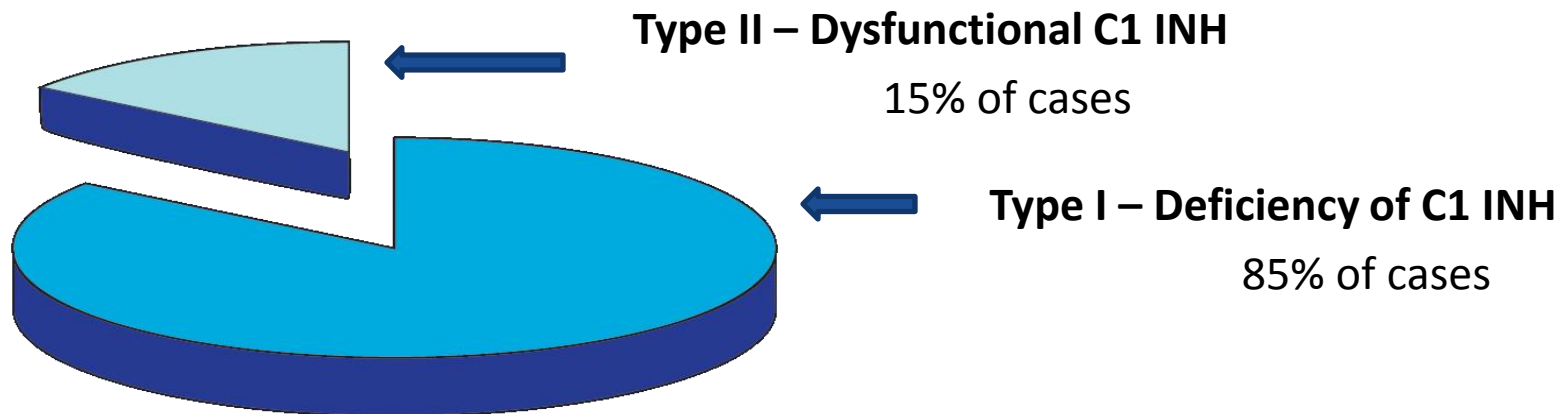
# Patient History Assists in Diagnosis

- Recurrent, unexplained swelling without urticaria
- Typically worsens at puberty
- Almost always abdominal
- Family history of HAE
  - 25% of patients have no prior family history
- First attack usually during first decade of life



# Laboratory Testing

- Laboratory tests are used for diagnosis, but are not relevant to monitor the disease or medication efficacy
- Screening test
  - C4 antigen (if normal, screen during attack)
- Follow-up tests
  - Antigenic C1 INH levels
  - Functional C1 INH levels



# Diagnosis

Diagnostic Test	Type 1 HAE	Type 2 HAE	AAE
C4, Serum	Low	Low	Low
C1 Inhibitor, Serum	Low	Normal or Increased	Normal or Low
C1 Inhibitor, Function	Low	Low	Low
C1q, quantitative	Normal	Normal	Low



# Management of HAE

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## Acute Therapy

# Therapy for Acute Attacks

## Support

- Supportive care
  - IV fluids
  - Airway maintenance
  - Analgesics
  - Anti-emetics
- Laryngeal attacks < 1% of all attacks, **BUT**
  - Greatest risk of mortality

**Airway**  
**Breathing**  
**Circulation**



# Therapy for Acute Attacks

## Pharmacologic

- Plasma-derived C1 INH
  - Available in Europe for 30 years
- Ecallantide (plasma kallikrein inhibitor)
- Icatibant (bradykinin B2 receptor antagonist )
- Fresh frozen plasma
  - Risk of exacerbation of attack
  - Not recommended in life-threatening situations
- Agents **not** recommended for acute attacks of HAE
  - Antihistamines
  - Glucocorticoids
  - Epinephrine
  - Antifibrinolytics
  - Androgens



# Plasma-Derived C1 INH

- Targeted therapy
  - Nanofiltered pasteurized concentrate C1 INH-nf (Cinryze®)
  - Pasteurized lyophilized concentrate C1 INH (Berinert®)
- Administered intravenously
- Multiple studies demonstrating effectiveness
  - Acute therapy
  - Prophylactic therapy
- European use for 30+ years
- Theoretical risk of blood borne pathogens



# Clinical Trials

## Cinryze<sup>®</sup>

- Manufactured by ViroPharma Inc.
- To evaluate nanofiltered C1 INH concentrate in the treatment of HAE
  - 68 patients with acute attacks randomly assigned
    - 35 patients received C1 INH
    - 33 patients received placebo
  - 1 or 2 intravenous injections of 1000 units each
- Primary endpoint was unequivocal relief of symptoms
  - Median time to onset was 2 hours in treated subjects
  - Median time to onset was > 4 hours in placebo group



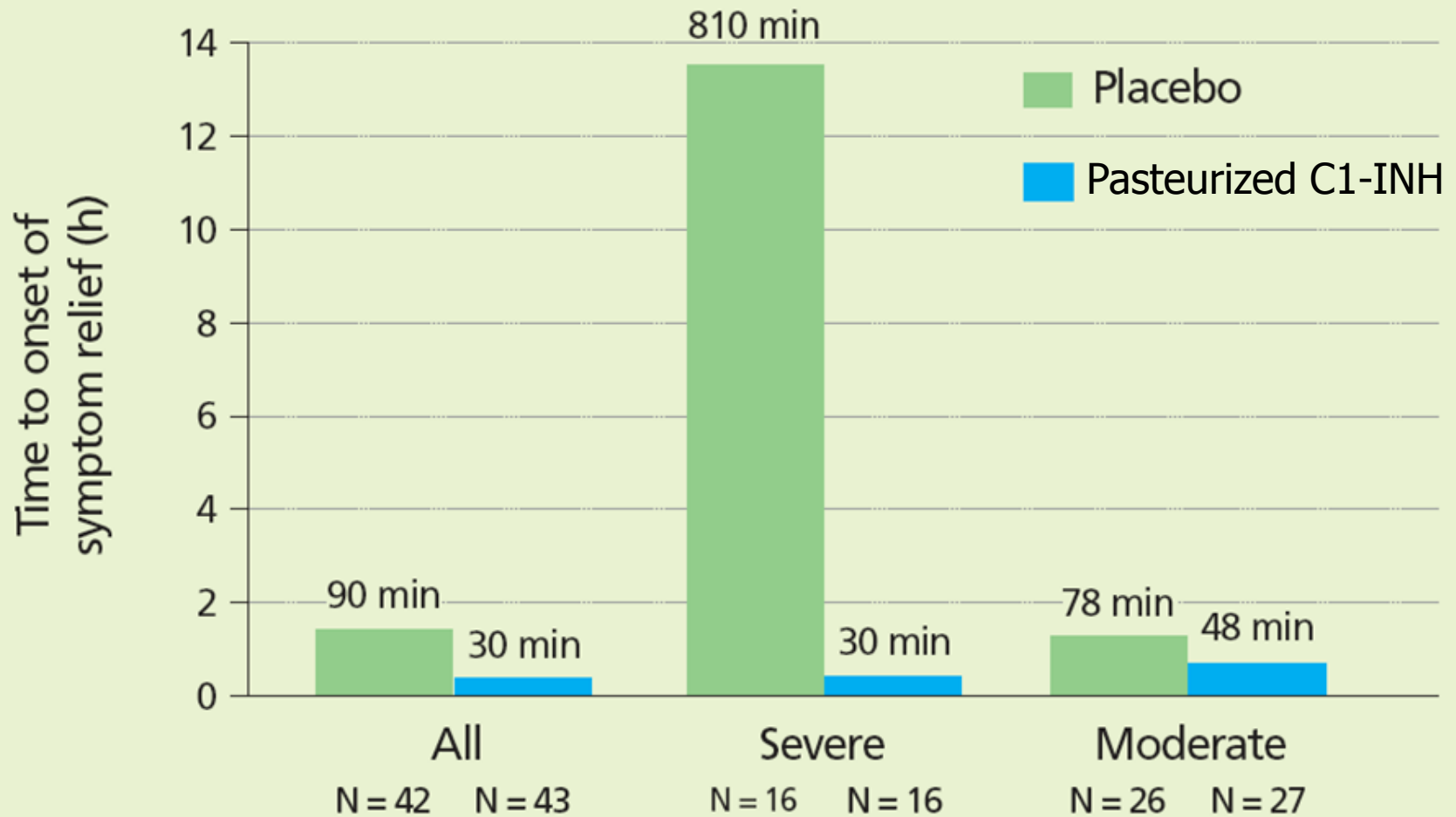
# Clinical Trials

## Beriner<sup>®</sup>

- Manufactured by CSL Behring
- 2007 phase III double-blind, placebo-controlled study: International Multicenter Prospective Angioedema C1-INH Trial (IMPACT)
  - 125 HAE patients enrolled (45 centers, 15 countries)
  - Acute facial or abdominal HAE attacks
  - Primary endpoint: time to onset of relief



# Pasteurized Plasma C1 INH Concentrate



# Recombinant Human C1 INH (rhC1 INH)

- Description
  - Purified recombinant transgenic C1 INH
  - rhC1 INH cDNA
  - rhC1 INH extracted from breast milk of transgenic rabbits
  - Identical to plasma C1 INH at protein level
  - Inhibits proteases same as plasma C1 INH
  - Can't rule out allergic reaction
- Half-Life
  - 3 hours
- Indication
  - Acute treatment



# Clinical Trials

## rhC1 INH

- Independent, randomized, saline controlled, double-blind
  - European
    - 16 patients received rhC1 INH
    - 16 patients received saline
  - North American
    - 13 patients received 100 units/kg rhC1 INH
    - 12 patients received 50 units/kg rhC1 INH
    - 13 patients received saline
- Intravenous
  - rhC1 INH at 100 units/kg and 50 units/kg
  - Saline
- Primary endpoint time to the beginning of relief of symptoms
  - Measured by visual analog scale score



# Ecallantide

- Description
  - Plasma kallikrein inhibitor
  - Administered via subcutaneous injection
- Half-Life
  - $2 \pm 0.5$  hours
- Indication
  - Acute treatment
- Adverse effects
  - Anaphylactic/anaphylactoid reactions in some patients; Unclear etiology
  - Gastrointestinal (diarrhea, abdominal pain, nausea)
  - Headache, fatigue
  - Abnormal results in tests of coagulation
    - Known effect on activated partial thromboplastin time
    - No patients with clinically significant bleeding



# Clinical Trials

## Ecallantide

- Double-blind, placebo-controlled studies
  - EDEMA3
    - 72 patients
    - Subcutaneous ecallantide vs. placebo
  - EDEMA4
    - 96 patients
    - Subcutaneous ecallantide vs. placebo
- Cutaneous, abdominal, facial attacks
- Both studies showed significant efficacy in meeting primary end-point of improved patient scores (N = 168 total, P = 0.021, P = 0.01)



# Icatibant

- Description
  - Second-generation bradykinin B2 receptor antagonist
  - Contains several unnatural amino acids
  - Corrects abnormality in C1 INH in -/- mice
  - Administered via subcutaneous injection
- Half-Life
  - ~2-4 hours
- Potential Indications
  - Acute treatment of HAE
  - Other indications being considered include liver cirrhosis, severe burns



# Clinical Trials

## Icatibant

- Two double-blind, placebo-controlled phase III studies: For Angioedema Subcutaneous Treatment (FAST-1/FAST-2)
  - FAST-1: US study; 56 HAE patients
  - FAST-2: European study; 72 HAE patients
- Primary endpoint: median time to beginning of improvement
  - FAST-1 (P = 0.14)
    - 2.5 hours with icatibant
    - 4.6 hours with placebo
  - FAST-2 (P < 0.001)
    - 2.0 hours with icatibant
    - 12 hours with tranexamic acid
- Approved in all EU countries for the treatment of HAE



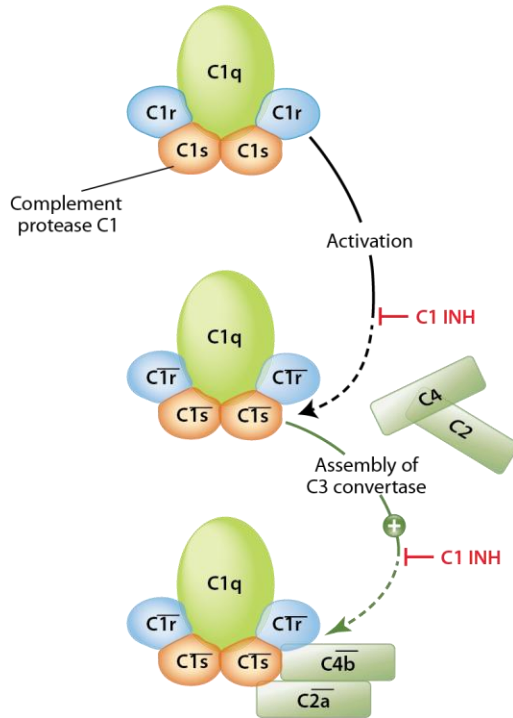
# FFP

- Has been used historically when other treatments unavailable
- Urticaria; anaphylactic shock; hemolysis; circulatory overload
- Disease transmission
  - Human immunodeficiency virus (HIV)
  - human T-cell lymphocytic virus (HTLV)
  - hepatitis B; hepatitis C
- Prions or nonenveloped viruses
  - Creutzfeldt - Jakob disease
  - hepatitis A
  - parvovirus

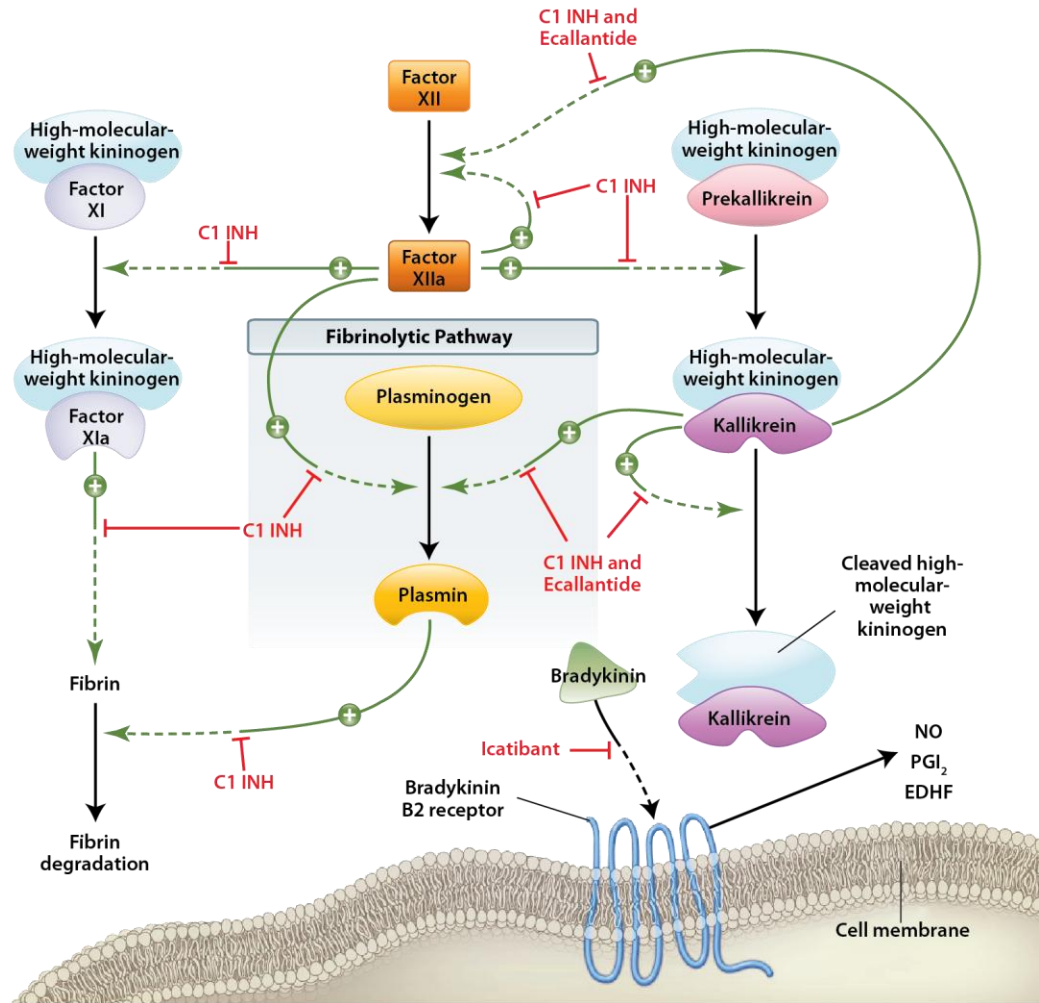


# Management of HAE

## Complement Pathway



## Contact Activation Pathway



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# Management of HAE

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## Routine Prophylaxis

# Individualization of Patient Care

- Based on close consultation between physician and patient to manage disease
  - Determine patient goals
  - Proactive approach **in advance** of acute attacks
- Individualized care
  - Management of clinical symptoms
  - Impact of disease on patient's life
  - Variability of disease
  - Prophylaxis is an important option



# Management Strategies

- C1 INH replacement
  - Indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE
- Danazol
  - Indicated for the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females
- Antifibrinolytic agents
  - Epsilon-aminocaproic acid
  - Tranexamic acid
  - Not approved for the treatment of HAE in the USA



# Cinryze<sup>®</sup> Routine Prophylaxis

- Crossover trial
- Compared prophylactic twice-weekly injections of 1000 units vs. placebo during two 12 week periods
- Primary endpoint was number of attacks
  - 6.26 attacks with C1 INH
  - 12.73 with placebo
  - $P = <0.001$
- Reduction in:
  - Frequency
  - Severity
  - Duration
  - Total number of days with swelling
  - Need for rescue



# Androgens

- Synthetic 17- $\alpha$ -alkylated androgens also known as attenuated or impeded androgens
  - Danazol
  - Stanozolol
  - Oxandrolone
- Theoretically increases hepatic production of C1 INH
- Contraindications
  - Undiagnosed abnormal genital bleeding
  - Markedly impaired hepatic, renal, or cardiac function
  - Pregnancy
  - Breast feeding



# Androgens: Side Effects

- Weight gain
- Lipid abnormalities
- Psychological effects
  - Nervousness
  - Emotional lability
- Women
  - Virilization, hair growth, menstrual irregularities, acne, voice deepening
- Hepatocellular abnormalities
  - Transaminase elevations
  - Adenoma
  - Carcinoma
- Thromboembolic events
- Hypertension
- Muscle or joint pain



# Antifibrinolytic Compounds

- Some efficacy in prophylaxis reported in open-label studies
- Epsilon-aminocaproic acid (EACA)
  - Severe long-term toxicity
- Tranexamic acid
  - Widely used in Europe
- Side effects include
  - Myalgia; muscle weakness
  - Rhabdomyolysis
  - Increased serum creatine phosphokinase or aldolase levels
  - Hypotension
  - Fatigue
  - Can interfere with red/green vision (tranexamic acid)



# Treatment Summary

- Current therapies
  - Agents for acute treatment of attacks
    - C1 INH / rhC1INH
    - Ecallantide
    - Icatibant
    - Fresh frozen plasma
  - Agents for routine prophylaxis
    - C1 INH
    - Androgens (danazol, stanozolol)
    - Antifibrinolytics
- Consideration criteria for prophylaxis include
  - Description and nature of attacks
  - Burden on activities of daily living



# Hereditary Angioedema

- HAE is a debilitating and potentially life-threatening condition affecting 1:10,000 to 1:50,000
- HAE imposes a significant burden of illness on patients and the healthcare system
- Diagnosis rests upon
  - knowledge of disease
  - suspicion
  - good history taking
  - appropriate laboratory evaluation



# Hereditary Angioedema

## Key Diagnostic Points

- Recurrent undiagnosed episodic abdominal or pelvic pain
- Angioedema with no pruritis or urticaria
- Family history of swelling or recurrent abdominal pain
- **Slow** onset - over 1-2 days
- Appropriate laboratory evaluation
- Knowledge:

**Think about HAE → Diagnosis !**



# Thank you

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