Corso di Laurea Magistrale in Biotecnologie Mediche
Università degli Studi di Napoli Federico II
Corso Integrato di Basi molecolari di patologie immunitarie e neurologiche

Urticaria and Angioedema

Maria Rosaria Galdiero, M.D. Ph.D

Assistant Professor of Internal Medicine
Center for Basic and Clinical Immunology Research (CISI)
Division of Allergy and Clinical Immunology
Department of Translational Medical Sciences

Urticaria

Skin condition characterized by sudden appearance of wheals (hives), angioedema or both

Wheal

- Central swelling of variable size, almost invariably surronded by a reflex erythema
- Itching or burning sensation
- Fleeting nature, with skin returning to its normal appearance, usually within 1-24h

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Urticaria

Angioedema

- Sudden, pronounced erythematous or skin-colored swelling of the lower dermis and subcutis with frequent involvement below mucous membranes
- Sometimes pain rather than itching
- Slower resolution (up to 72h)
- One third of chronic urticaria patients

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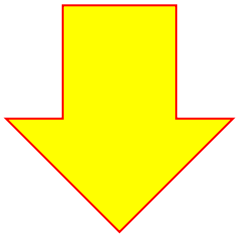
Angioedema

Urticaria and Angioedema

Physiopathology

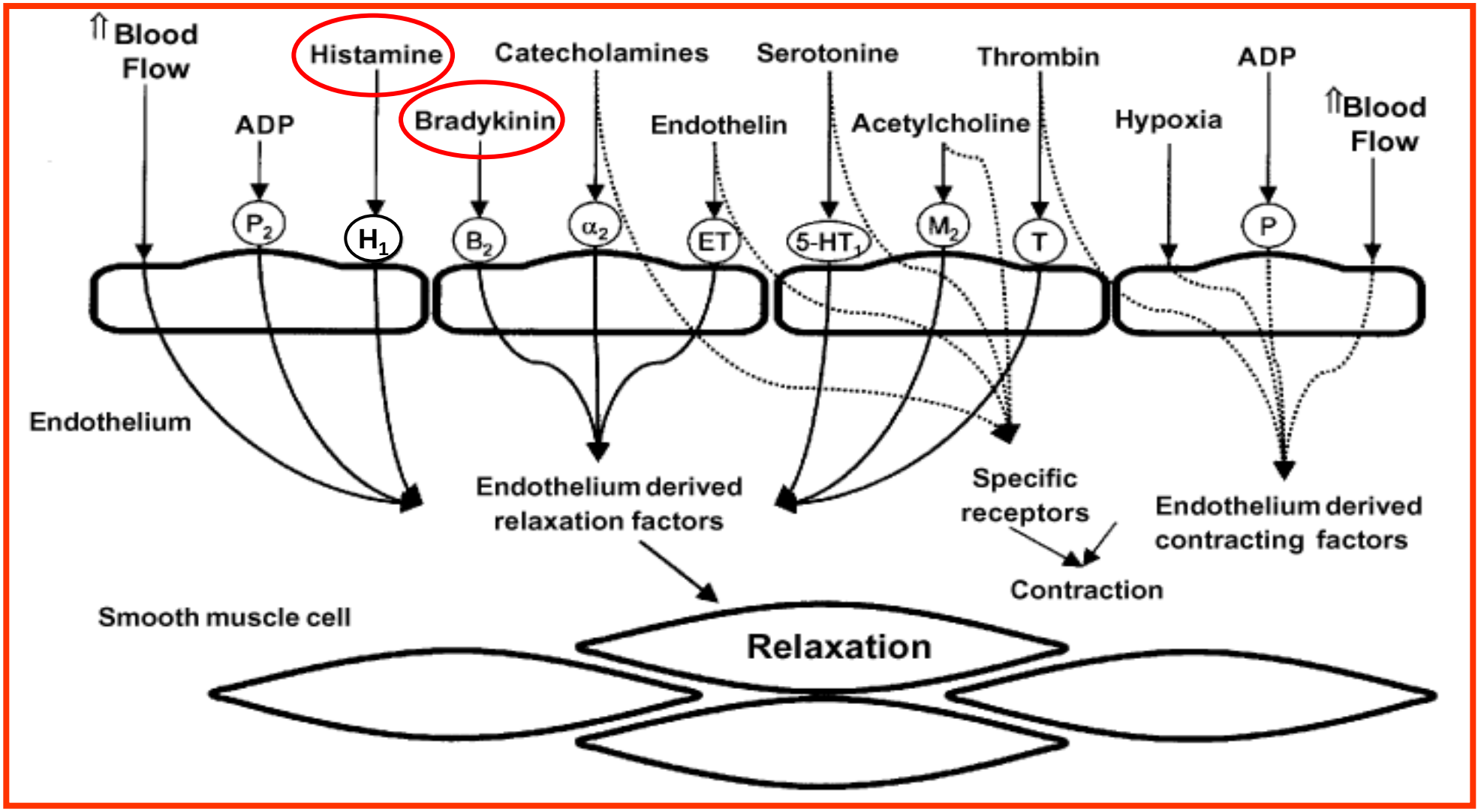
Due to the release of vasoreactive mediators:

histamine, Cysteinil-leukotrienes (LTC_4, LTD_4, LTE_4), Platelet-Activating Factor (PAF) from **cutaneous mast cells** or the release of **bradykinin** and complement factors:



Vasodilation and increased vascular permeability

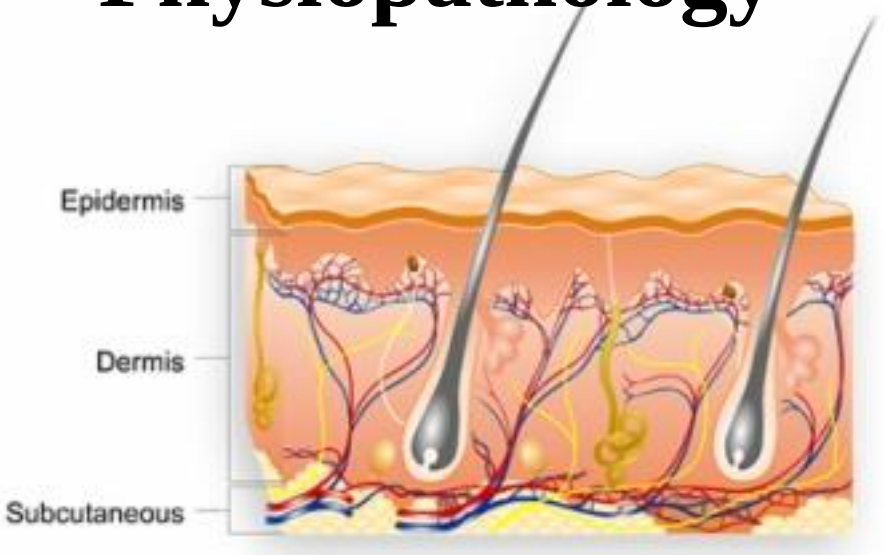
Vasodilating Mediators



Urticaria and Angioedema

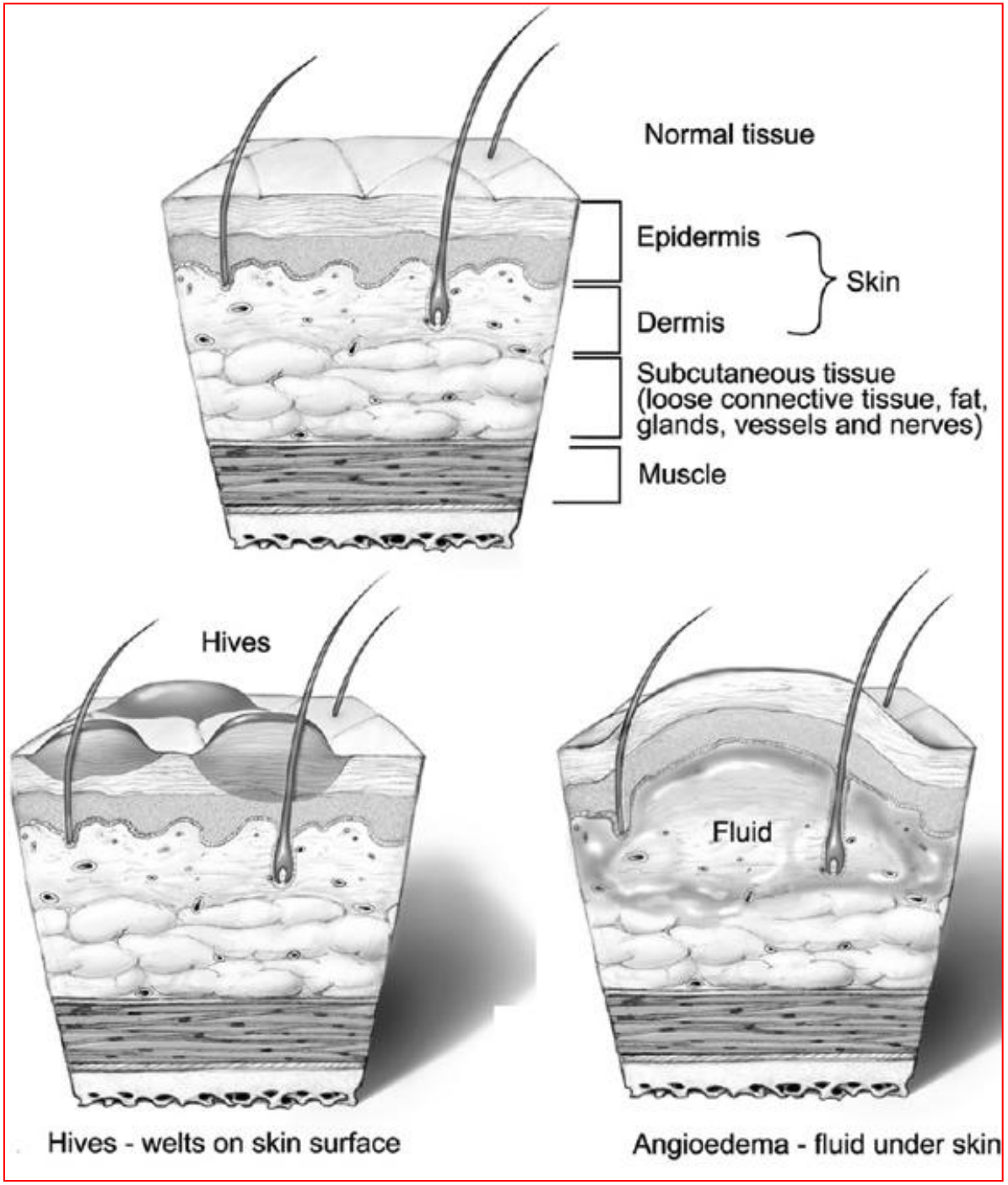
Physiopathology

Urticaria vs. Angioedema



Clinical Comparison of Features of Angioedema and Urticaria

Feature	Angioedema	Urticaria
Pathology	Reticular dermal, subcutaneous/submucosal edema +++, vasodilation +/-; little or no cellular infiltrate, except in allergic angioedema where eosinophils may be seen	Papillary dermal vasodilation +++, edema +, sparse perivascular infiltrate of mainly neutrophils, eosinophils, monocytes and T-lymphocytes
Clinical		
Location	Skin and mucosae	Skin only
Duration	1-5 days	Transitory (<24 h)
Color of lesions	Pink or skin colored	Red
Itch	Variable	Almost invariable
Pain, tenderness	Common	Rare


Normal tissue
Epidermis
Skin
Dermis
Subcutaneous tissue
(loose connective tissue, fat,
glands, vessels and nerves)
Muscle
Hives
Fluid
Hives - welts on skin surface
Angioedema - fluid under skin

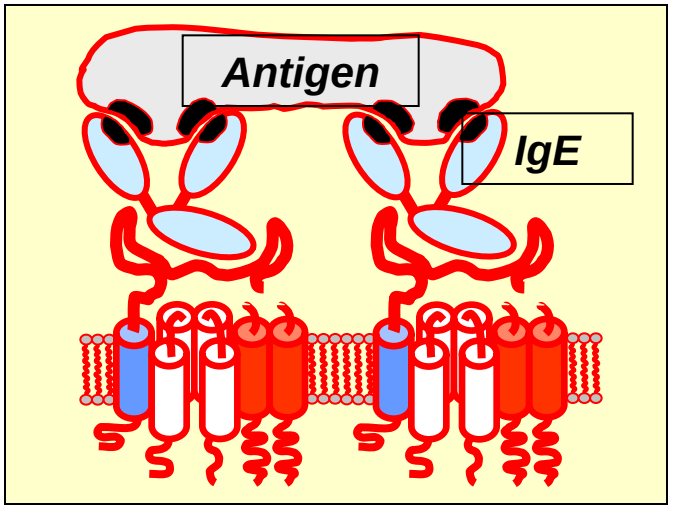
Immuno-mediated Urticaria

Type I Hypersensitivity Reactions (IgE-mediated)

- **Food-induced** (especially peanuts, eggs, nuts and shellfish)
- **Drug-induced** such as antibiotics

  (especially penicillin and sulfa), aspirin and ibuprofen
- **Parasitic infestations**

  (Ascaris, Tenia, Giardia, Anchylostoma)
- **Insect stings or bites**
- **Pet dander**
- **Pollen**
- **Latex**



Food-induced Urticaria

Acute	Rapidly occurs after ingestion
Chronic (rare)	Lasts for at least six weeks
Contact	Occurs as a result of skin contact with a food In some cases is associated with angioedema
Food dependent exercise induced	Combination of food trigger plus exercise trigger

Drug-induced Urticaria

- Acute onset
- Potential pathogenic mechanisms:
  - IgE-mediated
  - histamine release
  - cyclooxygenase and lipoxygenase unbalance
  - Complement activation
- **Drugs responsible:**
  - Acetylsalicylic acid and NSAID
  - Antibiotics
  - Iodinated contrast media
  - Blood and plasma derivatives
  - Anesthetics
  - Oral contraceptive

Immuno-mediated Urticaria

Type II Hypersensitivity reactions (Antibodies-mediated)

- **Transfusion reactions**
  (unmatched blood type and/or immunoglobulin infusion)

Type III Hypersensitivity reactions (immunocomplexes)

- **Urticaria Vasculitis**
- **Urticaria in autoimmune diseases**
  (Crioglobulinemia, Hashimoto thyroiditis, Coeliac disease, Type I diabetes, etc.)
- **Immunoglobulin and/or plasma derivatives infusions**

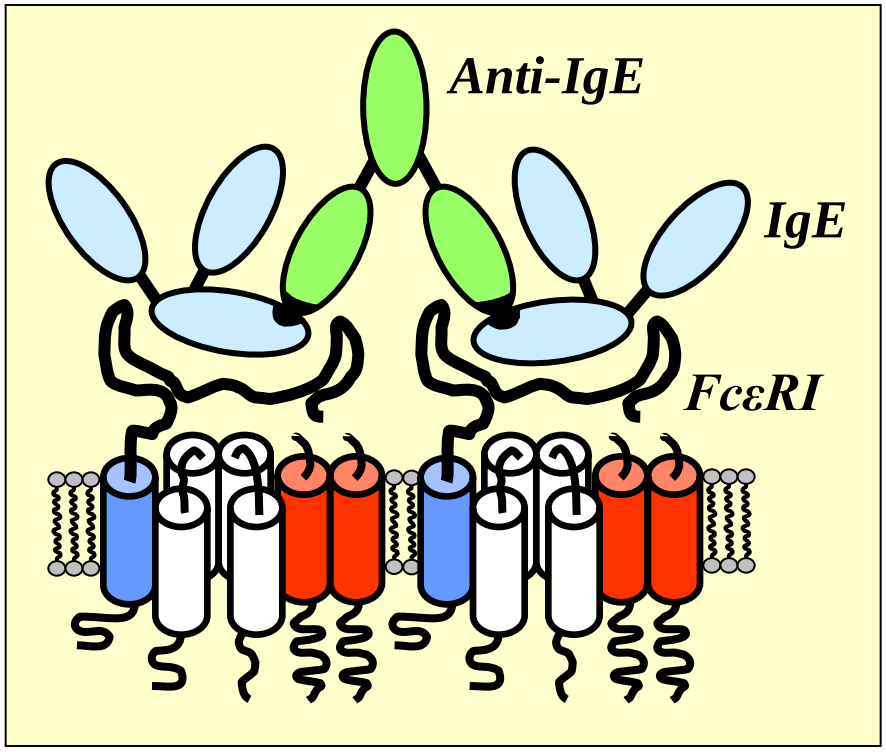
Type IV Hypersensitivity reactions

- **Contact dependent urticaria**

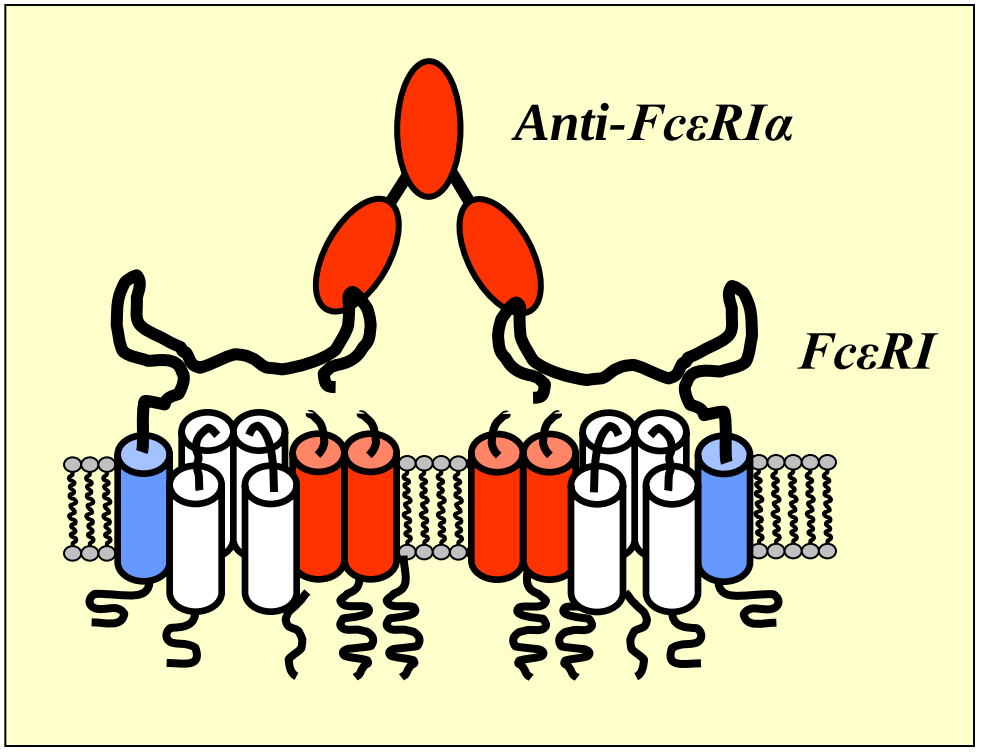
Immuno-mediated Urticaria

Autoimmune Chronic Urticaria

Anti-IgE Antibodies



Anti-FcεRI Antibodies



Others…

Undefined Immuno-mediated Chronic Urticaria

- **Infectious diseases**
  - **Bacteria** *(Streptococci, Staphilococci, Helicobacter Pylori)*
  - **Viruses** *(Hepatitis ABC, HIV, EBV, HSV, CMV, Coxsackie)*
  - **Parasites** *(Giardia Lamblia, Entamoeba, Trichinella)*
- **Neoplasias**
  - **Lymphomas, Leukemias, solid cancers**

Non immuno-mediated Chronic Urticaria

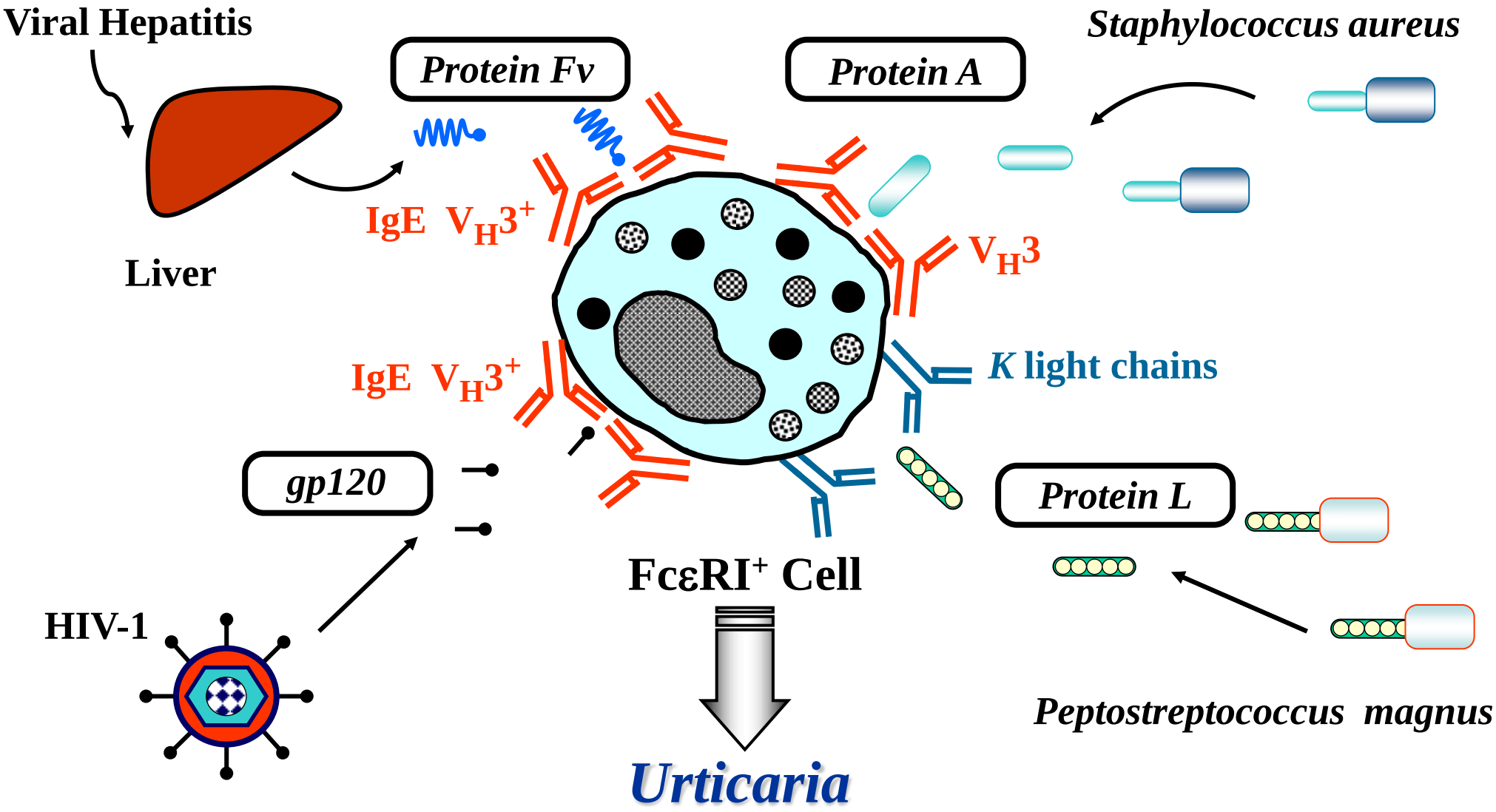
- **Physical** *(cold, heat, vibratory, pressure, solar, dermographic, acquagenic, cholinergic)*
- **Histamine-liberating substances** *(food, drugs, irritants)*

Urticaria Pigmentosa (Mastocitosis)

Chronic Spontaneous Urticaria (CSU)

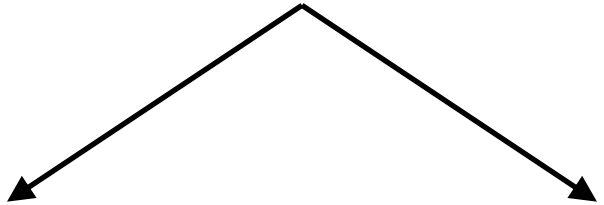
Pathogenetic Link between Endogenous, Viral and Bacterial

Superallergens and Urticaria



Clin. Exp. Allergy Rev. 4: 64, 2004

Urticaria



Acute

< 6 weeks

Allergic
(food, drugs, insect stings, radio contrast agents, transient viral infections)

Chronic

> 6 weeks

- Underlying cause NEVER allergy
- Positive autoimmune serology (ATA, ANA)

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Chronic Spontaneous Urticaria

Epidemiology and Impact of the disease

- Estimated lifetime prevalence 0.5-1%

- The impact of the disease:
  - disability
  - decreased quality of life
  - psycological and emotional distress
  - negative effects on sleep, daily activities, school/work and social interactions
  - decreased productivity

Difficult to treat

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Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI

POSITION PAPER

The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update

T. Zuberbier[1], W. Aberer[2], R. Asero[3], C. Bindslev-Jensen[4], Z. Brzoza[5], G. W. Canonica[6], M. K. Church[1], L. F. Ensina[7], A. Giménez-Arnau[8], K. Godse[9], M. Gonçalo[10], C. Grattan[11], J. Hebert[12], M. Hide[13], A. Kaplan[14], A. Kapp[15], A. H. Abdul Latiff[16], P. Mathelier-Fusade[17], M. Metz[1], A. Nast[1], S. S. Saini[18], M. Sánchez-Borges[19], P. Schmid-Grendelmeier[20], F. E. R. Simons[21], P. Staubach[22], G. Sussman[23], E. Toubi[24], G. A. Vena[25], B. Wedi[15], X. J. Zhu[26] & M. Maurer[1]

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Chronic Urticaria

Classification

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria	**Inducible Urticaria**
Spontaneous appearance of wheals, angioedema or both > 6 weeks due to known or unknown causes	Symptomatic dermographism* Cold Urticaria^ Delayed pressure urticaria^^ Solar urticaria § Heat urticaria Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria
*also called *urticaria factitia*, dermographic urticaria; ^also called cold contact urticaria; ^^Also called pressure urticaria; § also called heat contact urticaria	

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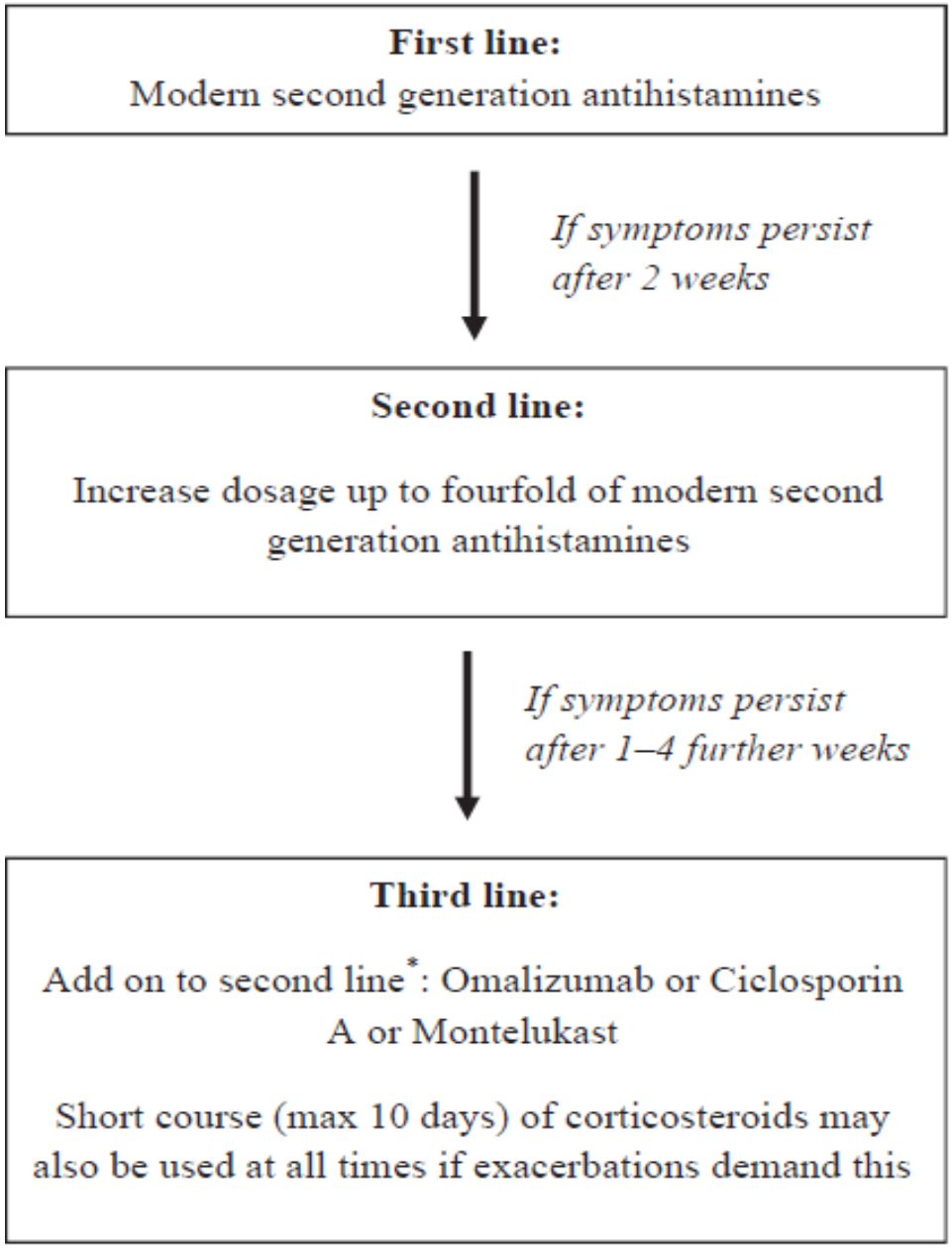
New international guidelines on the therapeutic approach to chronic urticaria



50%

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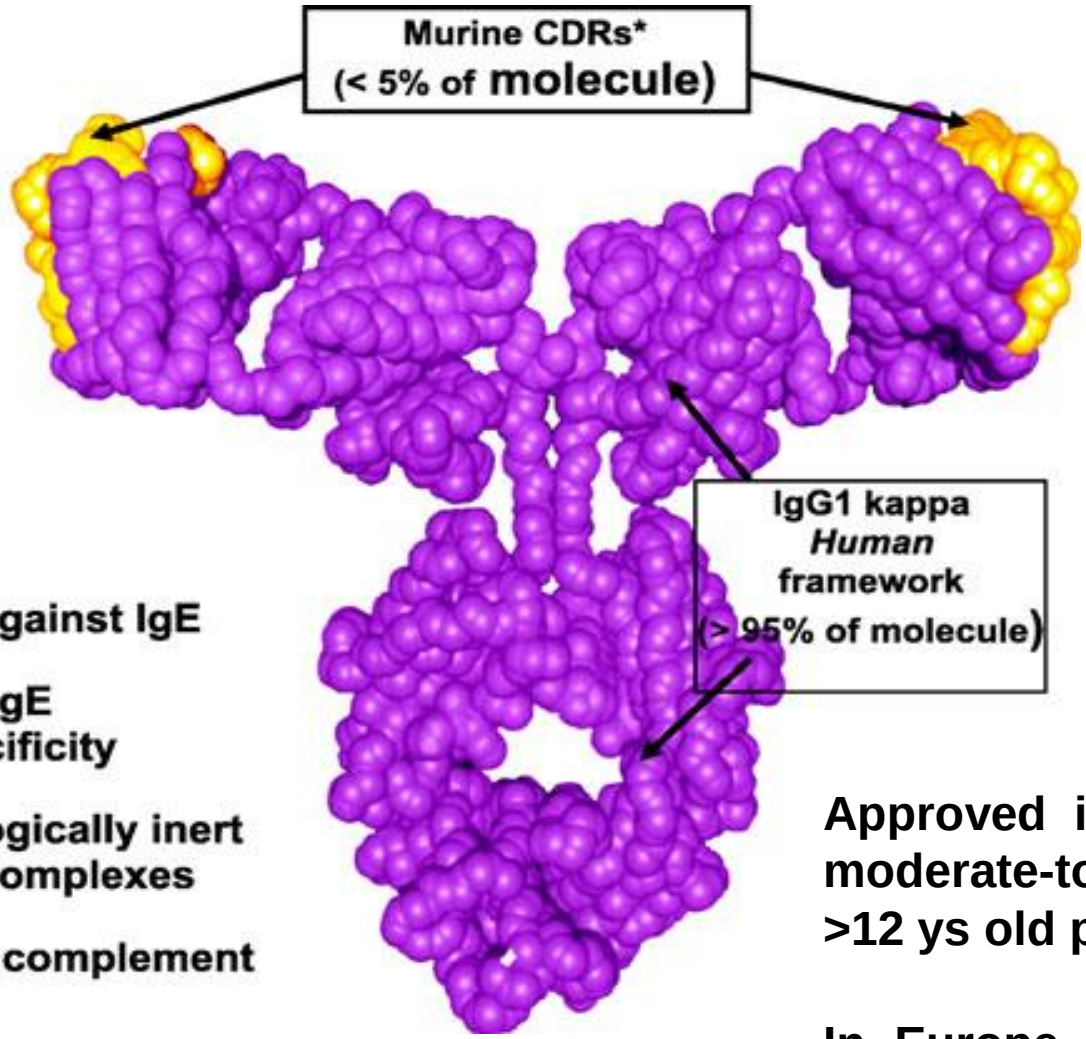
Is omalizumab useful in the treatment of patients unresponsive to high doses of H1-antihistamines as third-line treatment?

We recommend a trial of omalizumab as add on therapy to modern second generation H1-antihistamines as third-line in the algorithm of treatment of urticaria (strong recommendation/high level of evidence).

OMALIZUMAB



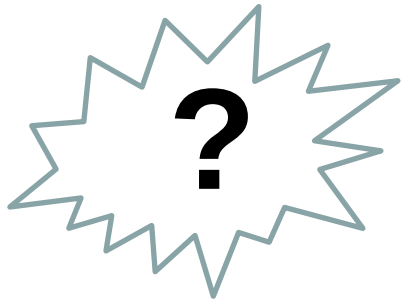
- Humanized mAb against IgE
- Binds circulating IgE regardless of specificity
- Forms small, biologically inert Omalizumab:IgE complexes
- Does not activate complement

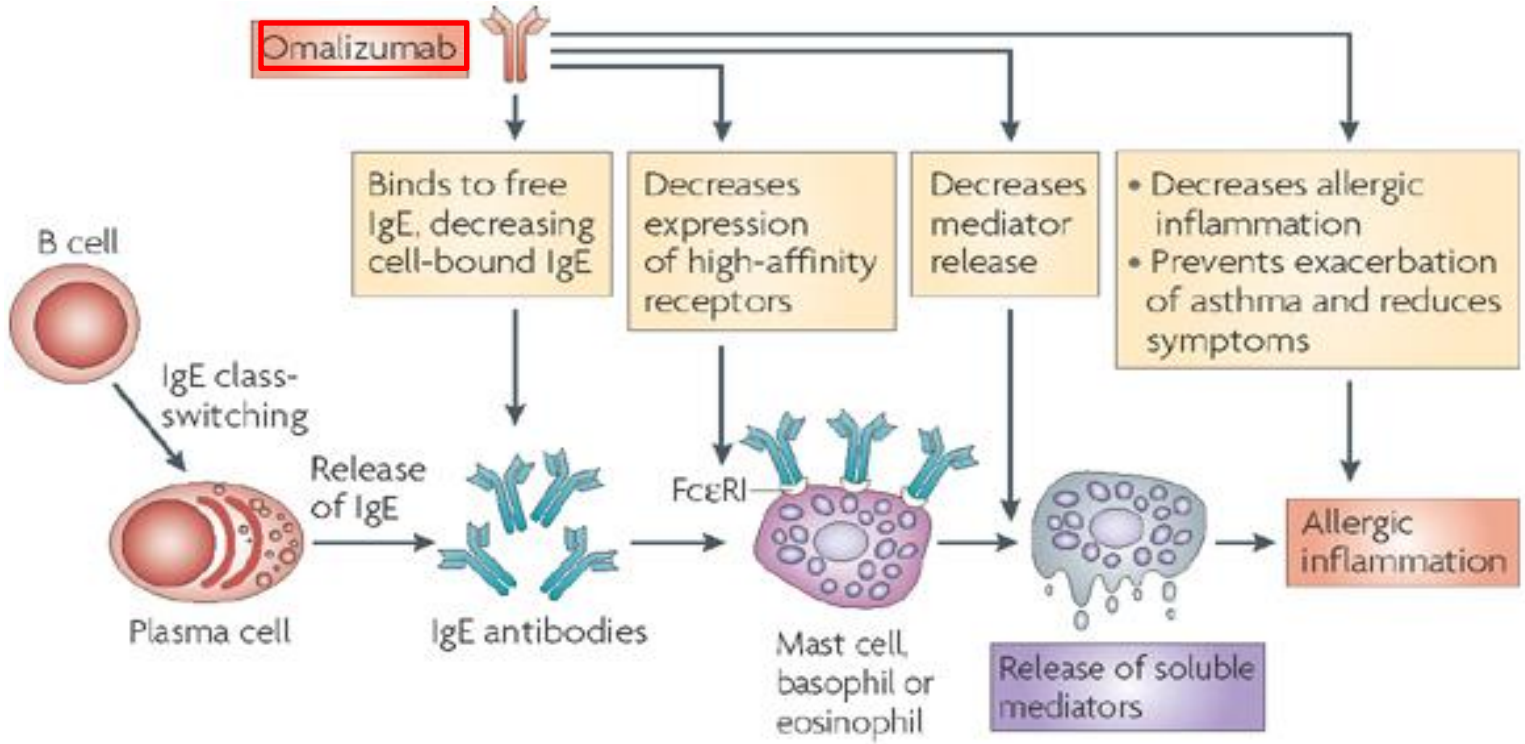
Approved in 2003 in USA for moderate-to-severe asthma in >12 ys old pts

In Europe in 2005 for severe allergic asthma in >6 yrs old pts

Treatment strategies for allergy and asthma

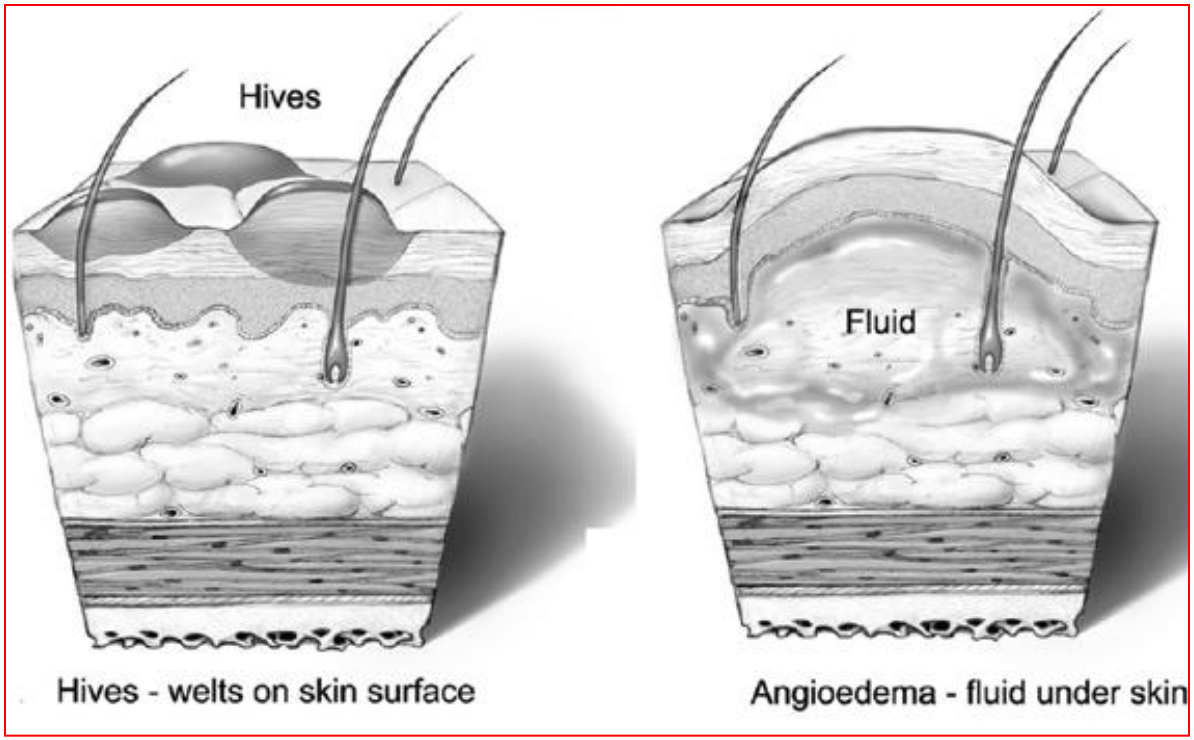
Stephen T. Holgate and Riccardo Polosa‡*





Angioedema

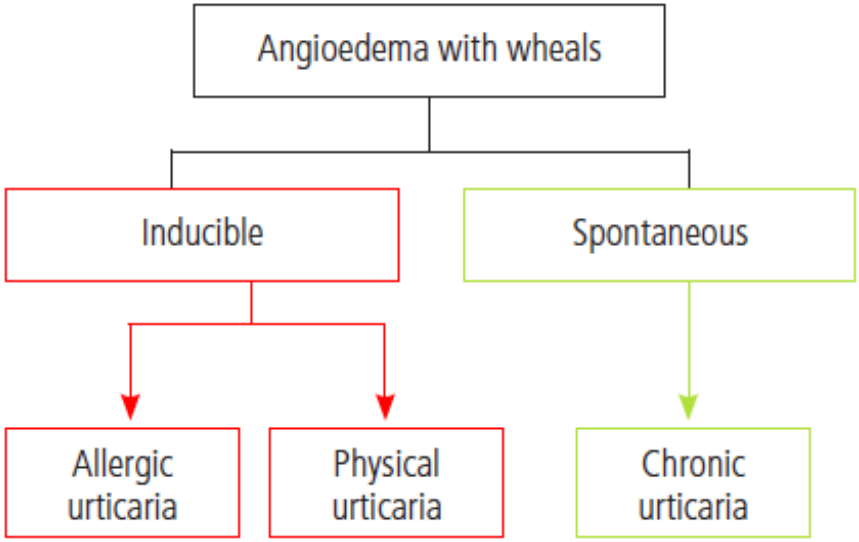
- Local non inflammatory, self-limiting edema owing to increased leakage of plasma from the capillaries located in the deep layers of the skin



- The leakage depends on accumulation of endogenous inflammatory compounds that increase endothelial cell permeability without a full-blown inflammatory process

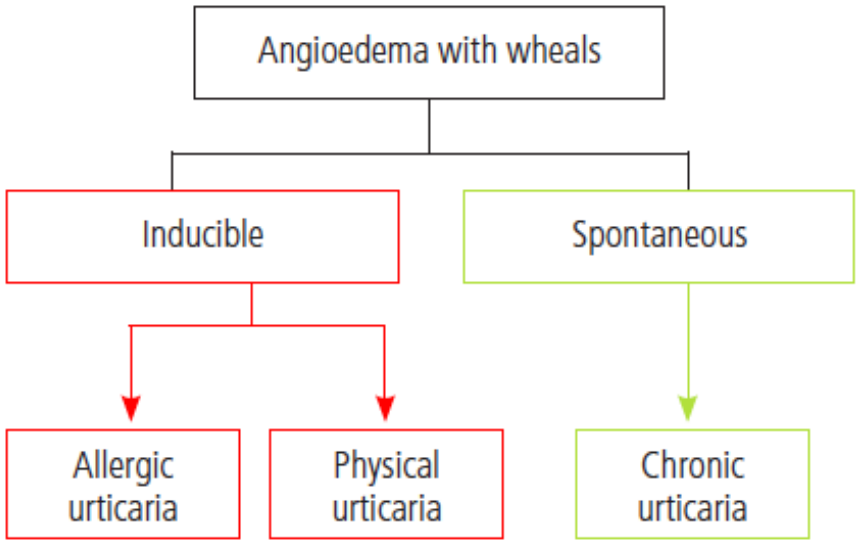
Angioedema

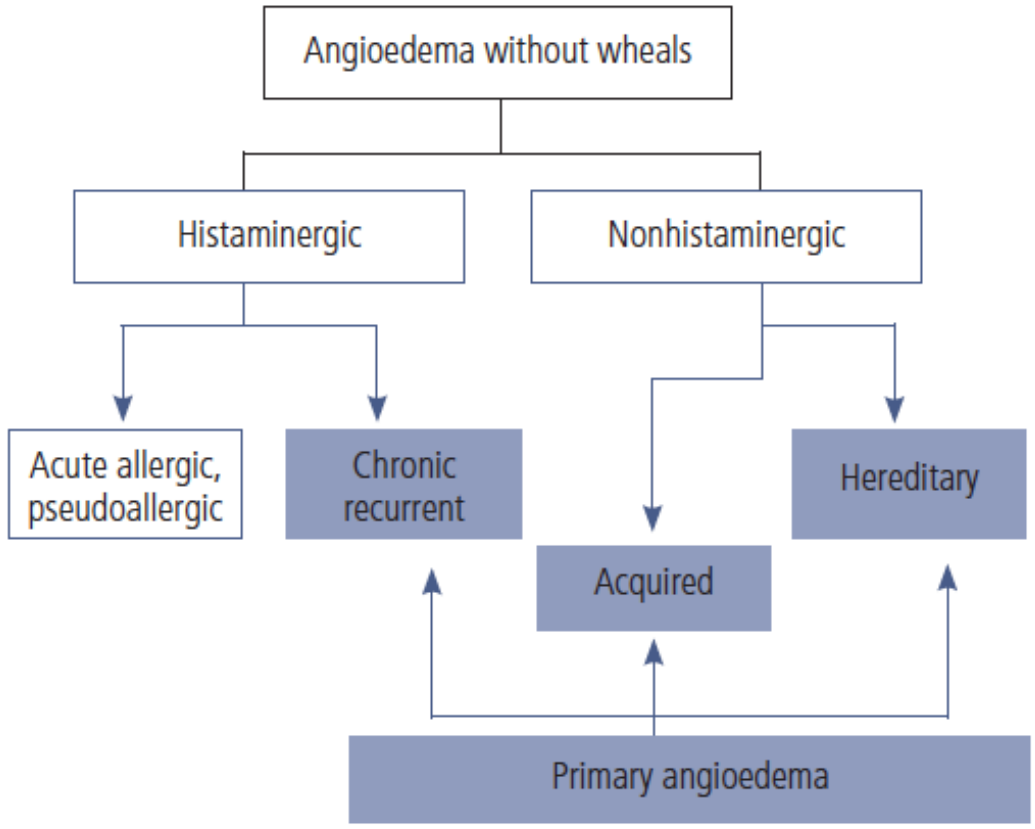
Angioedema



J Investig Allergol Clin Immunol 2016; Vol. 26(4): 212-221

Angioedema





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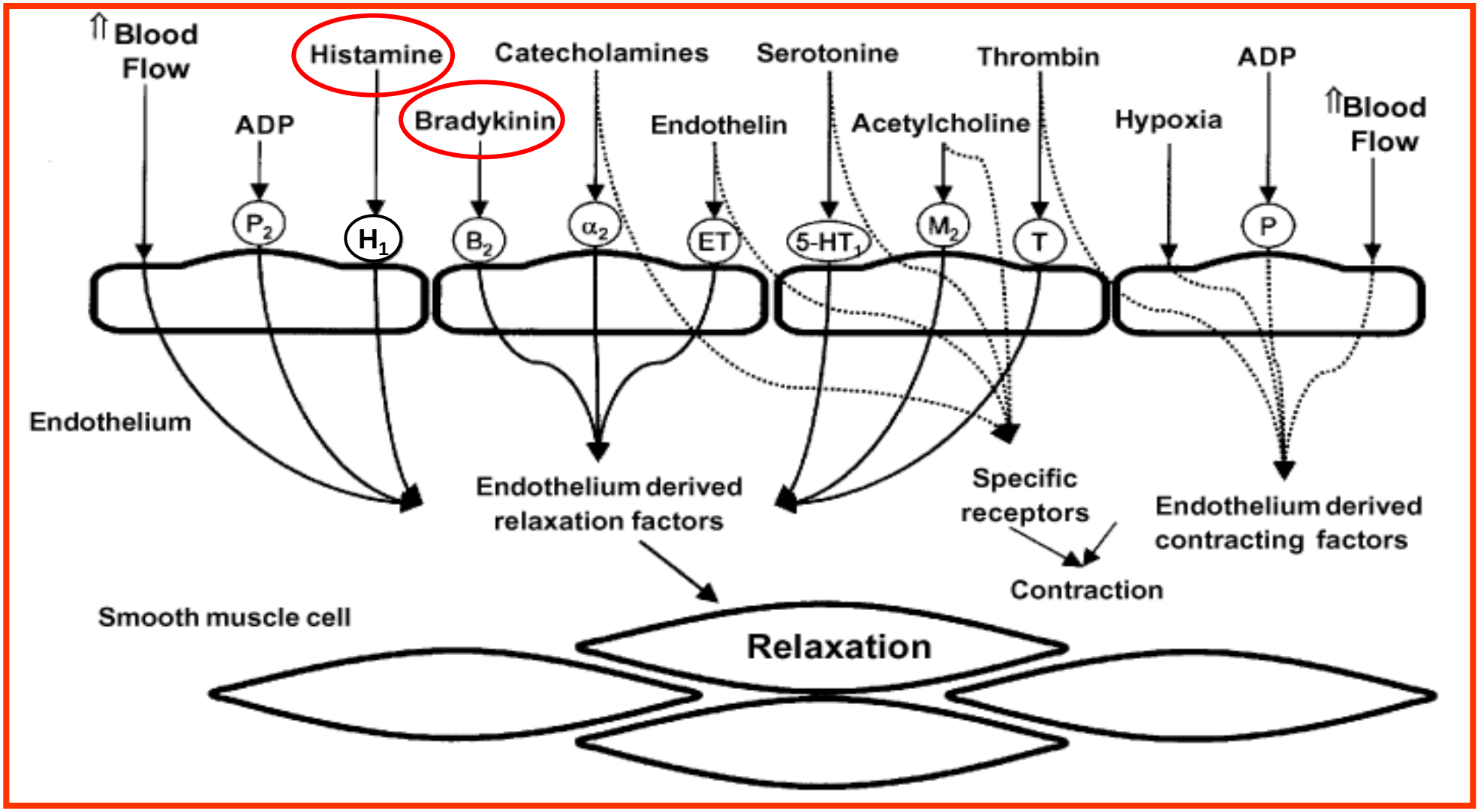
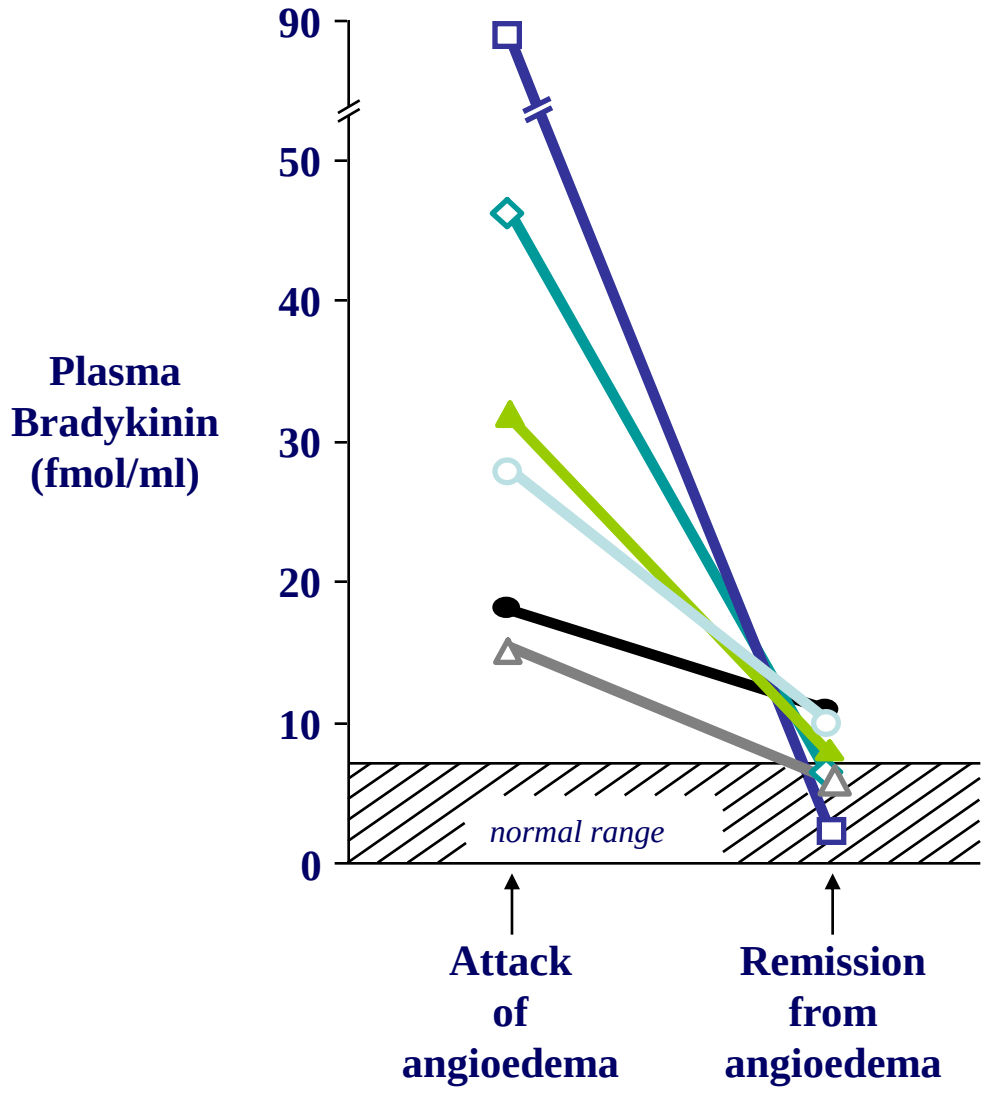
Vasodilating Mediators

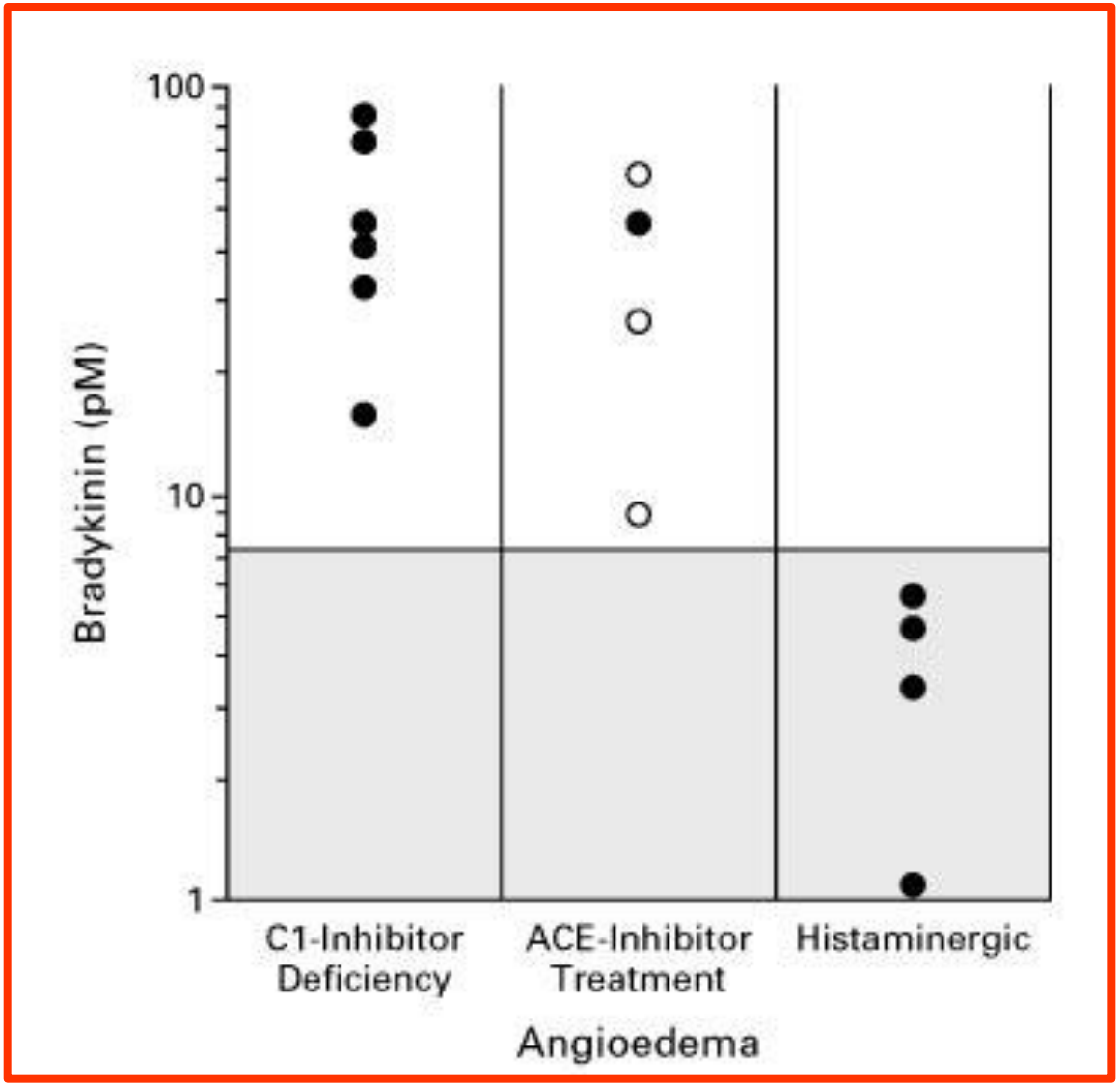


Plasma Bradykinin During Acute Attack of Angioedema and in Remission



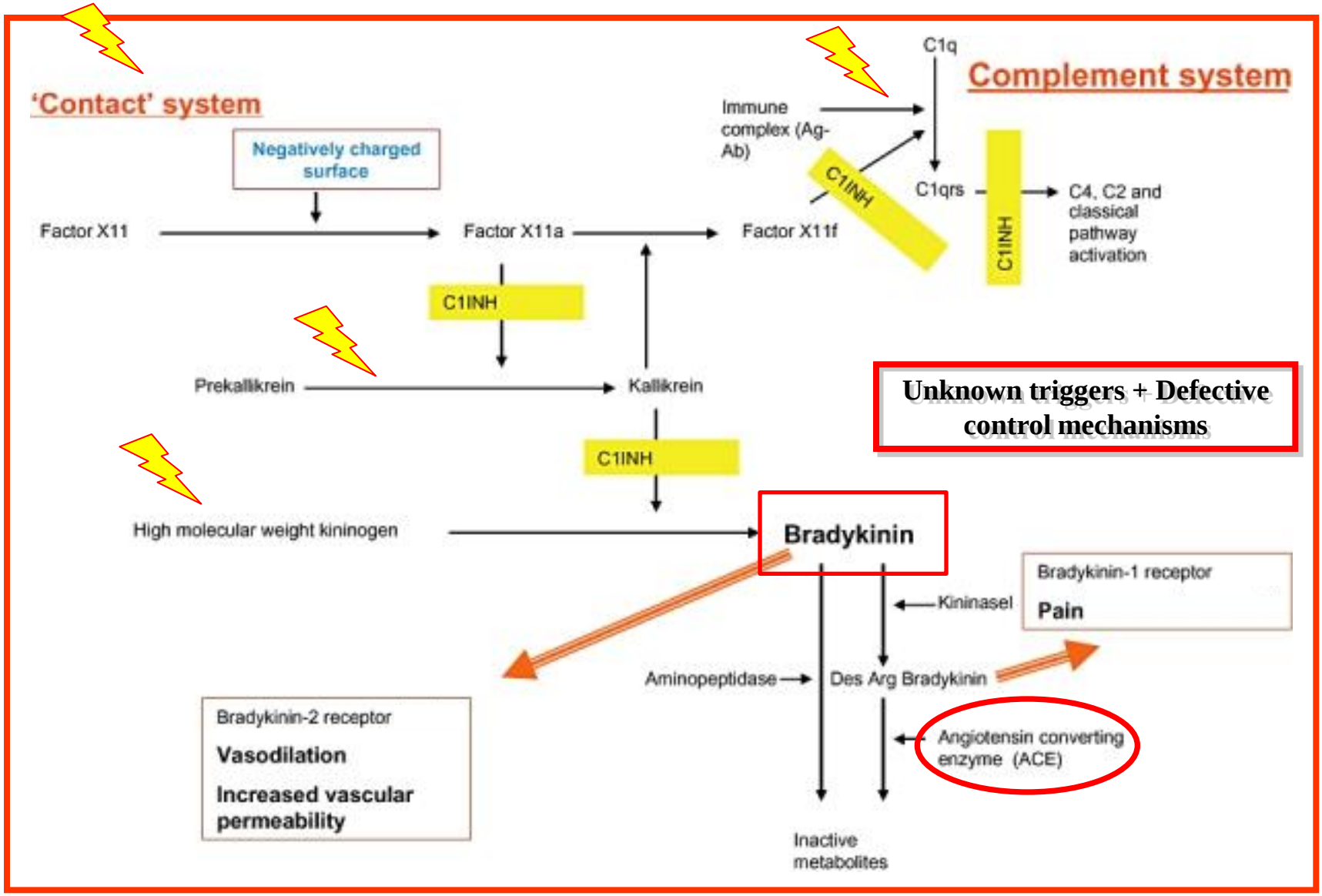
Lancet 1998; 351: 1693-1697

Plasma Bradykinin Levels in Patients with Different Forms of Angioedema



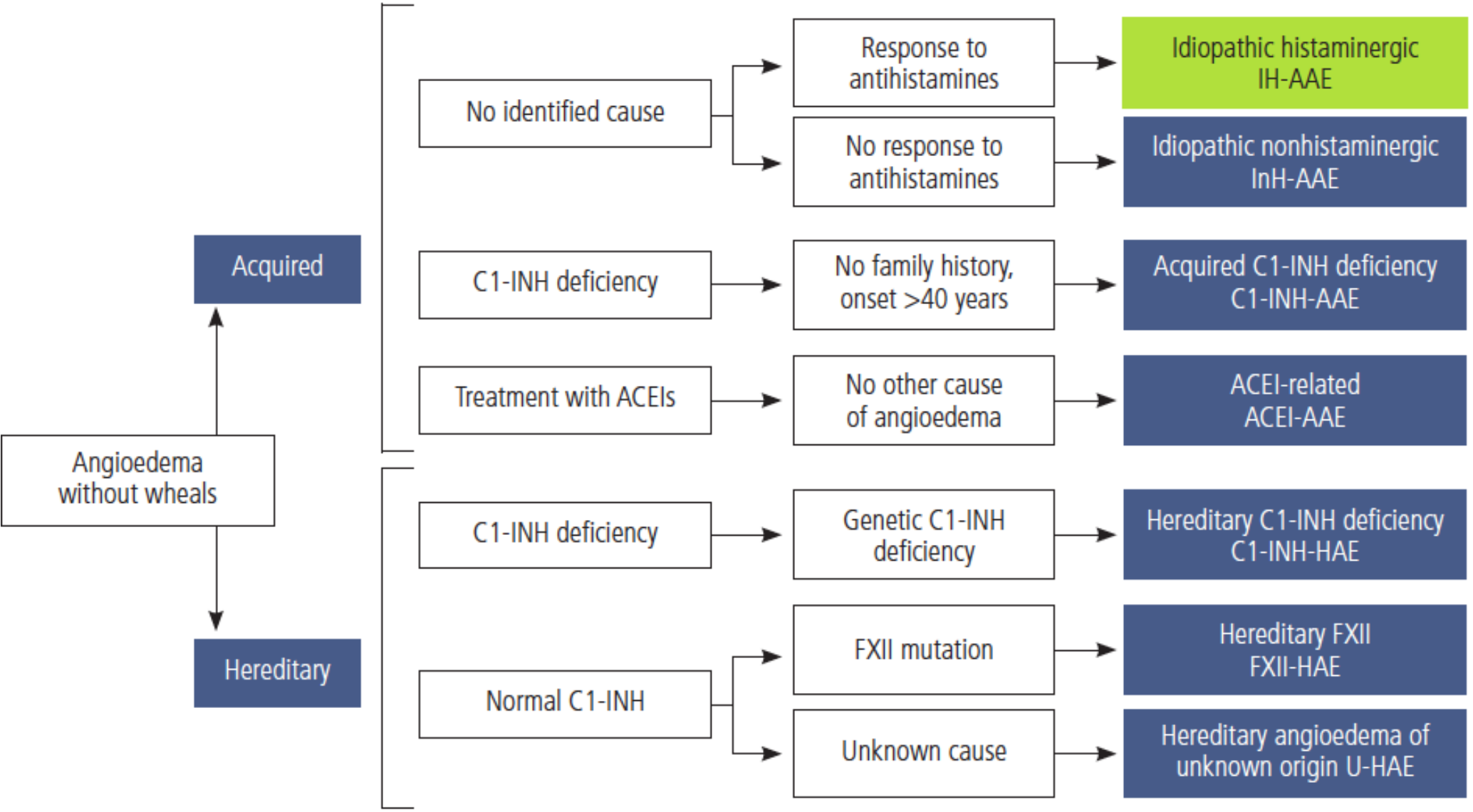
Nussberger *et al.* N. Engl. J. Med. 347: 621, 2002

Bradykinin-mediated Angioedema



Grigoriadou S. and Longhurst H.J. Clin. Exp. Immun. 155: 367, 2009

Angioedema without wheals



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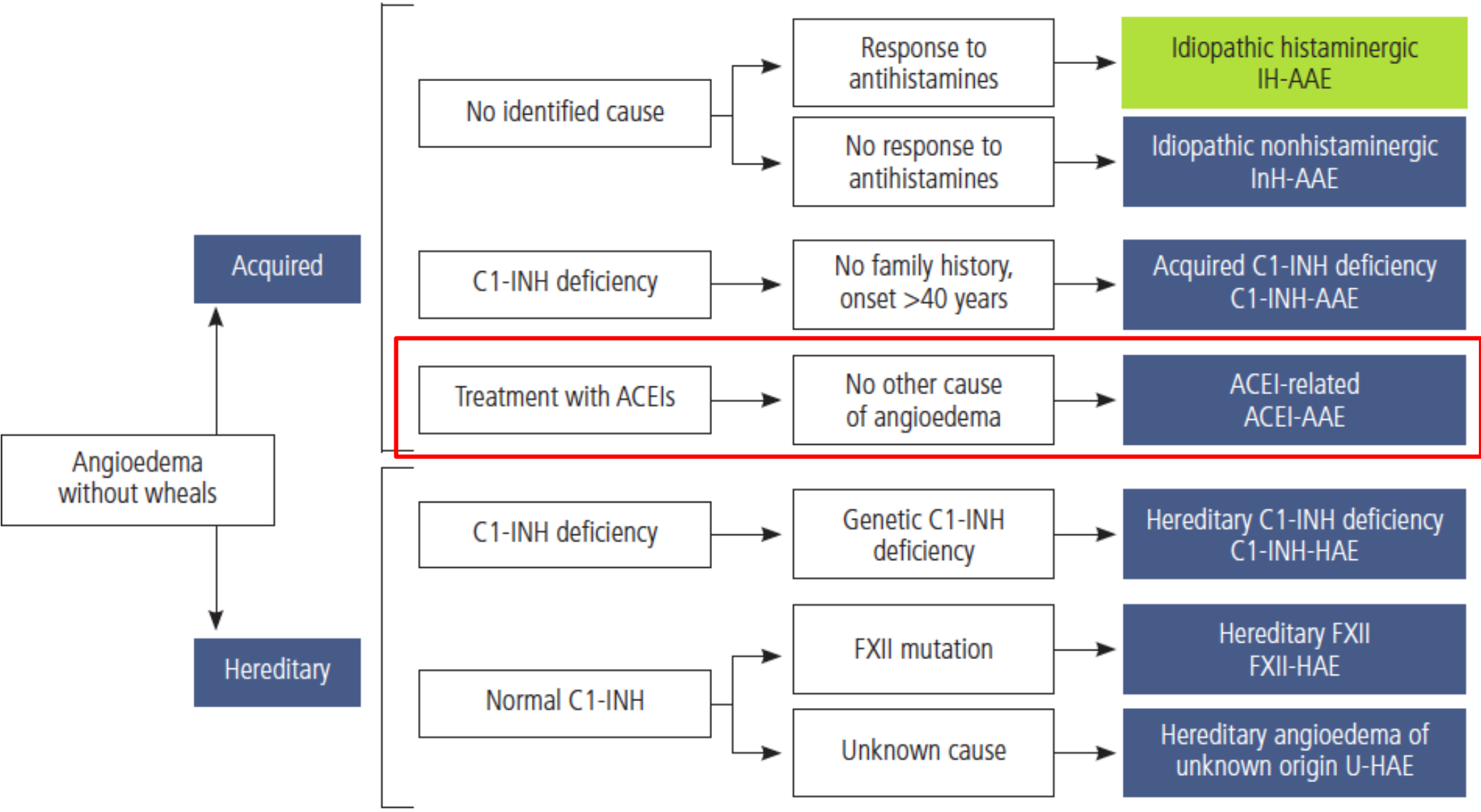
Angioedema without wheals



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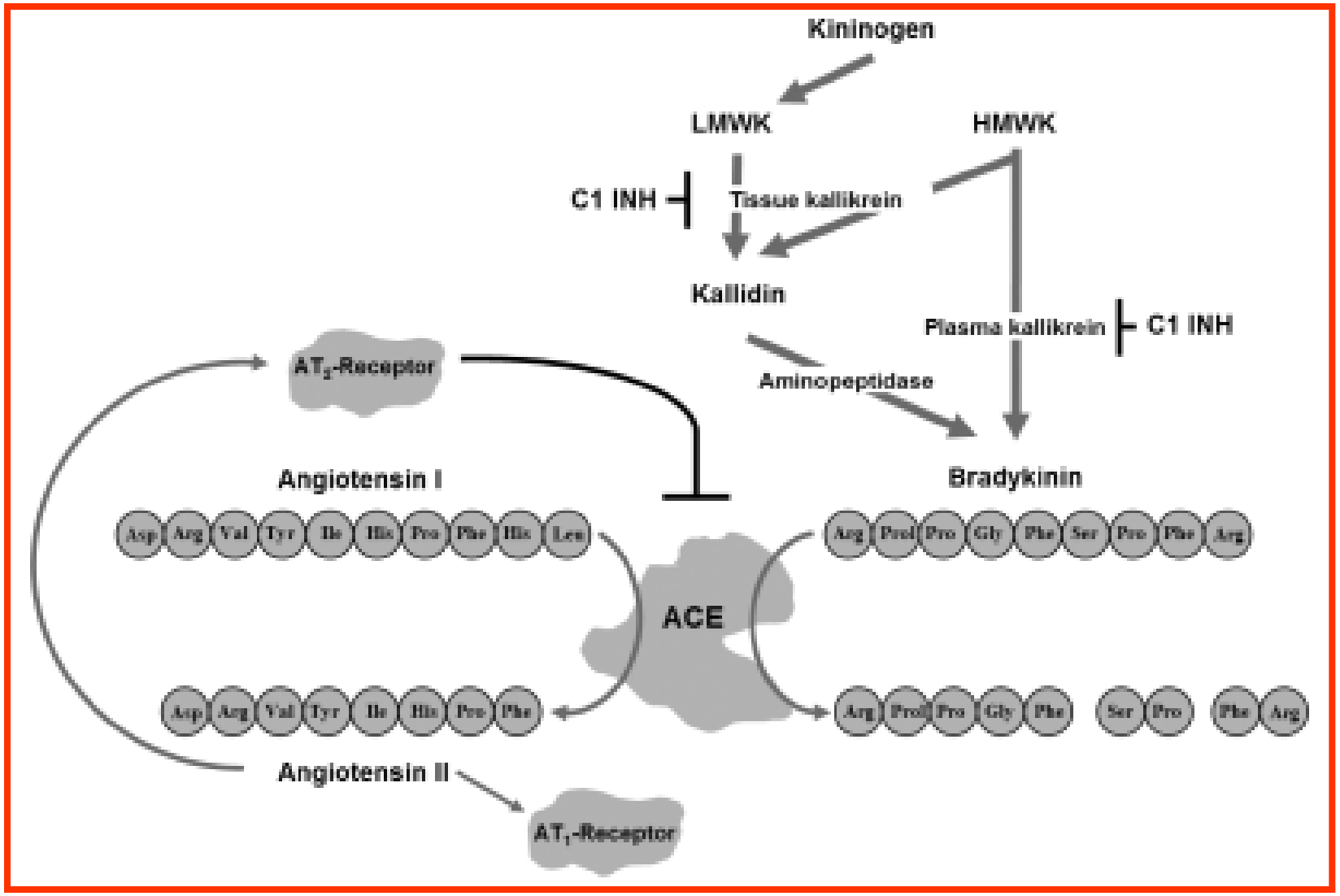
ACE-Inhibitors Acquired Angioedema (ACEI-AAE)

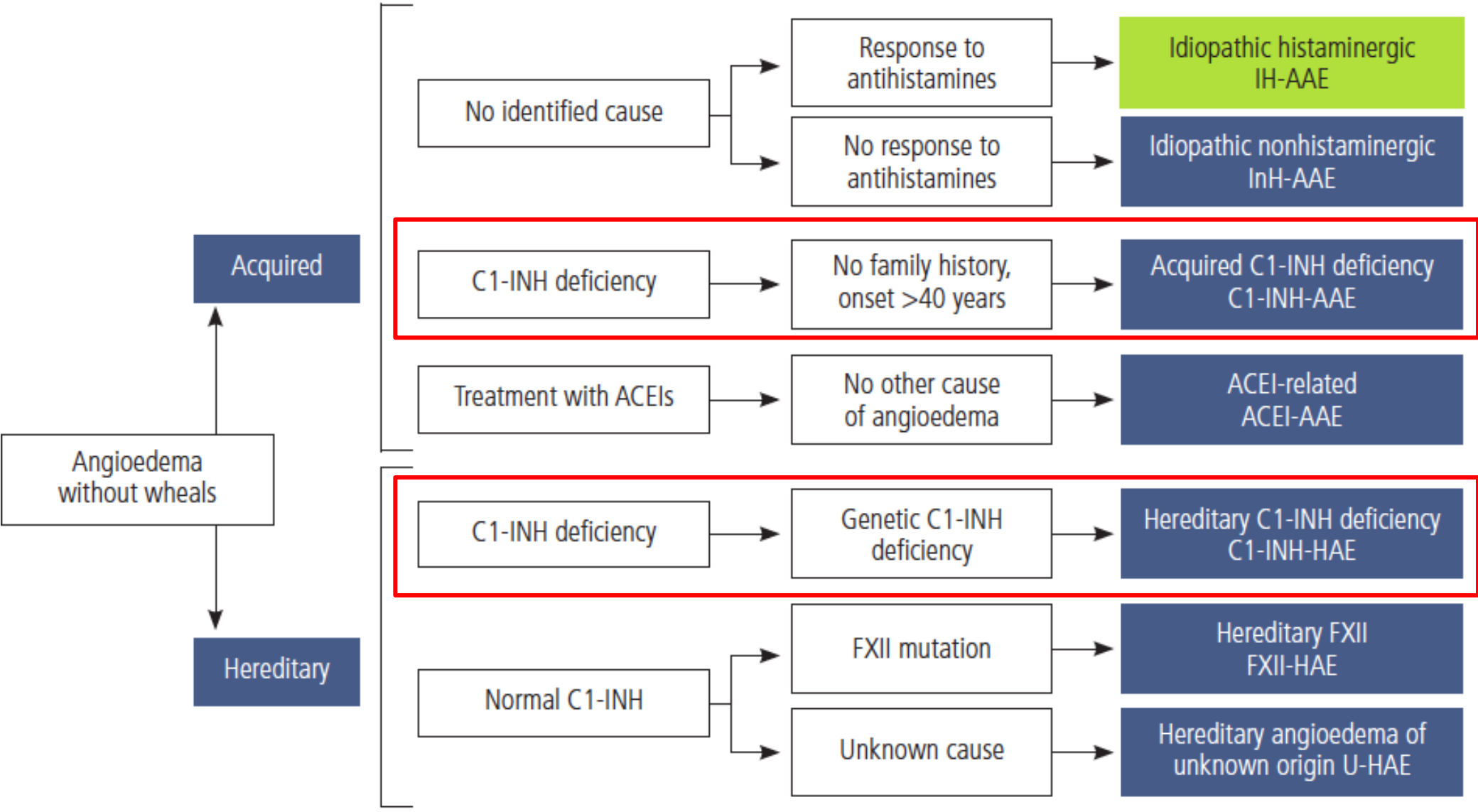
- **30-60% of drug-induced acquired angioedema**
- **0,7-1 % of ACEI treated patients experience ACEI-AAE**
- **Symptoms may start years after initiation of therapy and can recur with a varying frequency**
- **Increasing frequency and severity**
- **Frequently under diagnosed**
- **When treatment is withdrawn swelling stops or decrease significantly, even though 25% of patients continue to experience recurrence**
- **Bradikinin is known as the main mediator responsible, since ACE is the main physiologic pathway of BK degradation**

Connection between the Renin-Angiotensin System and the Kallikrein System



Bas *et al.* Allergy 62: 842, 2007

Angioedema without wheals



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C1 Inhibitor (C1-INH)

- **Member of the Serpin family (serin protease inhibitors)**
- **Chromosom 11 (q12-q13.1)**
- **>120 known genetic mutations (point mutations ≈ 85% or genetic rearrangement ≈ 15%)**
- **Serum normal levels: 15-20 mg/dl**
- **Controls the complement cascade activation in multiple points**

C1 Inhibitor (C1-INH) deficiency Angioedema

1. Acquired Angioedema

(due to protein consumption or anti-C1 INH antibodies)

- association with B-cell disorders (from monoclonal bands of uncertain significance to non Hodgkin lymphomas)
- diagnosis requires functional levels of C1-INH <50% of normal and C4 consumption
- in 70% of patients reduced C1q levels and anti-C1INH autoantibodies are detectable

2. HereditaryAngioedema ≈ 80% of cases

Type I (deficient synthesis of C1 INH) ≈ 65% of cases

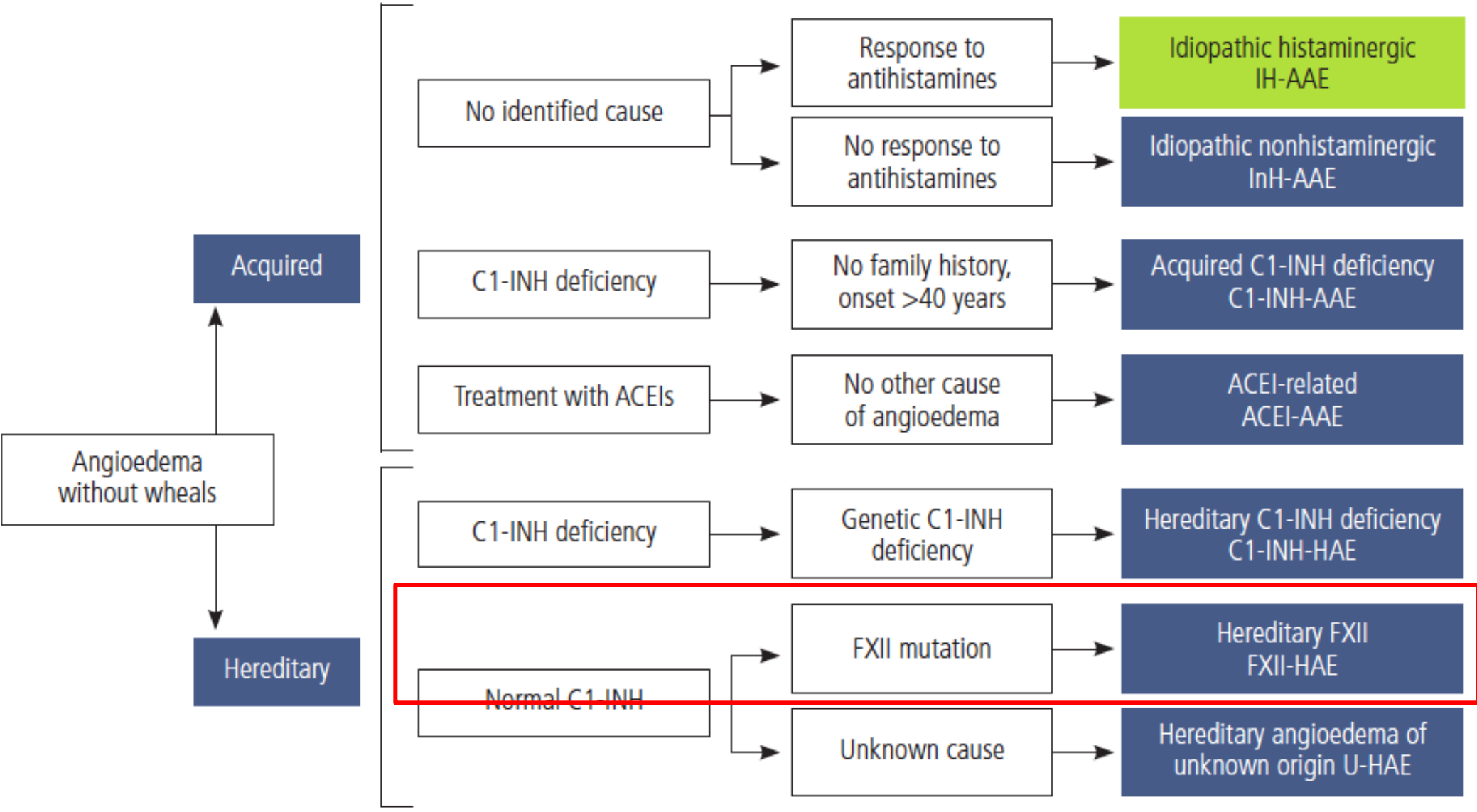
Type II (deficient functionality of C1 INH) ≈ 15% of cases

Tipo IIa (normal levels of antigenic C1 INH)

Tipo IIb (increases levels of antigenic C1 INH)

Type III (HAE of unknown origin)

Angioedema without wheals



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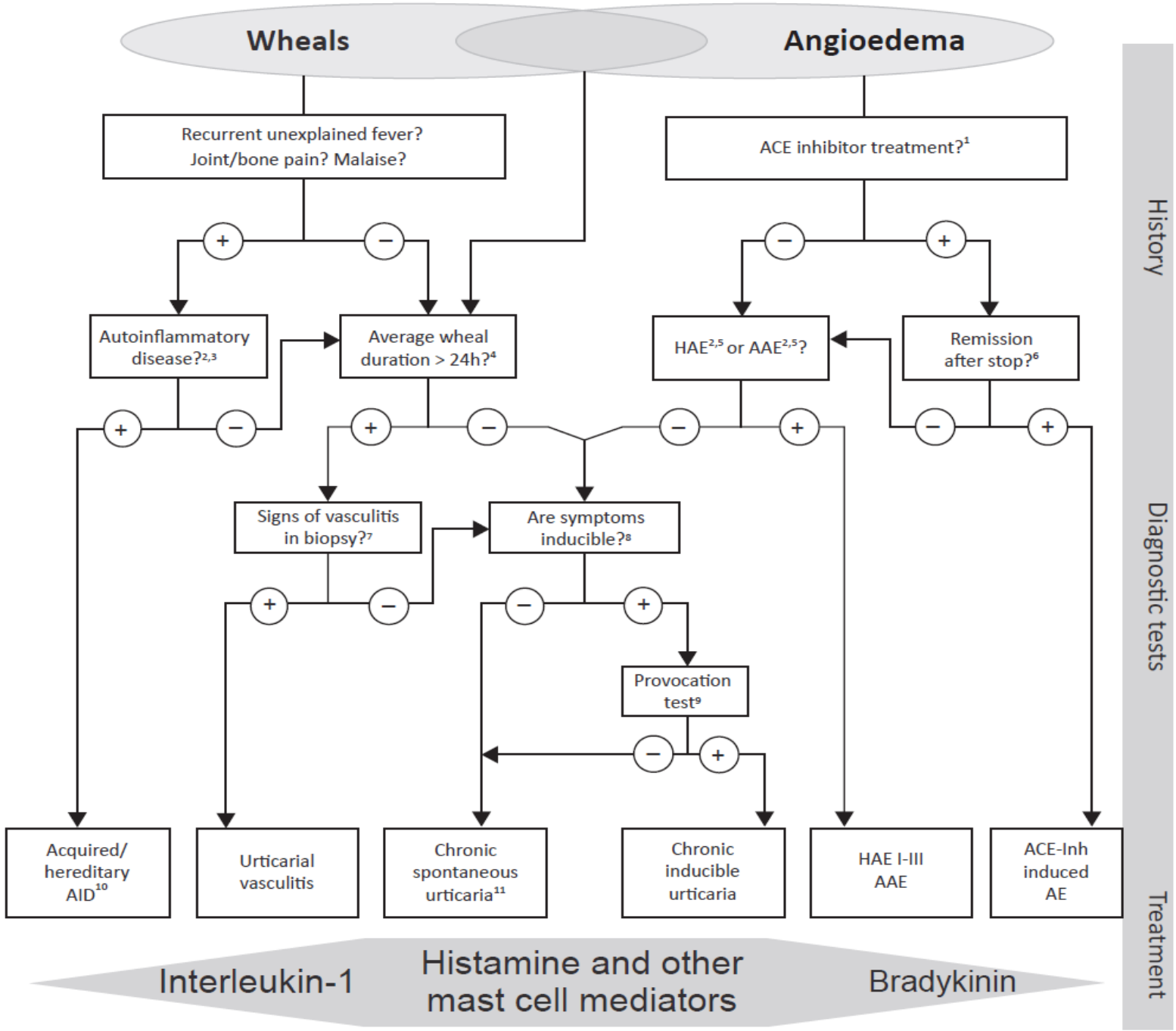
Hereditary Angioedema

- First described by H. Quincke in 1882 and better characterized by W. Osler in 1988
- Autosomal dominant patter of inheritance
- 10% of cases does not present family history and is due to *de novo* mutations
- HAE occurs < 20 years of age in 80% of cases
- It is characterized by recurrent attacks of edema without wheals and affects different areas of the body
- Attacks can be triggered by local trauma, surgical procedures, dental care, delivery, stress
- Duration of each attack ranges between 1 and 5 days


Wheals
Angioedema
Recurrent unexplained fever? Joint/bone pain? Malaise?
ACE inhibitor treatment?[1]
Autoinflammatory disease?[2,3]
Average wheal duration > 24h?[4]
HAE[2,5] or AAE[2,5]?
Remission after stop?[6]
Signs of vasculitis in biopsy?[7]
Are symptoms inducible?[8]
Provocation test[9]
Acquired/ hereditary AID[10]
Urticarial vasculitis
Chronic spontaneous urticaria[11]
Chronic inducible urticaria
HAE I-III AAE
ACE-Inh induced AE
Interleukin-1
Histamine and other mast cell mediators
Bradykinin
History
Diagnostic tests
Treatment

Treatment of Acute Attacks

- **Histaminergic :** Antihistamines,

  CCS, epinephrine

- **NonHistaminergic :** C1INH replacement

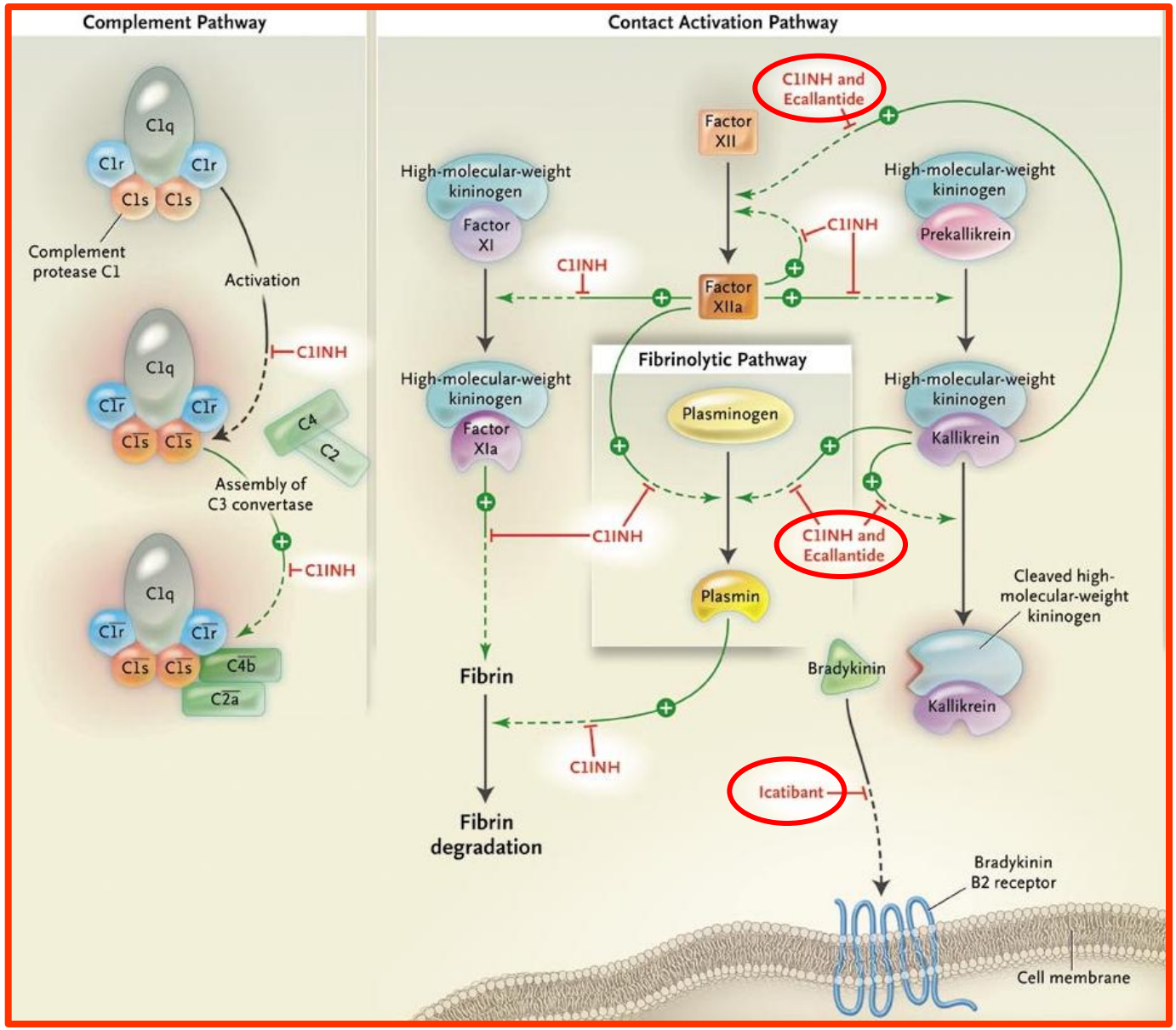
  blockade BK-B2R

  Inhibition of plasma kallikrein

Treatment of Acute Attacks

C1-INH concentrate or human recombinant e.v. shortens the duration of the attacks

Pathways Inhibited by C1-INH and New Drugs



Zuraw *et al.* N. Engl. J. Med. 359: 1027, 2008

Pharmacologic Therapy of acute attacks in HAE (FAST-1 and FAST-2 Trials)

- **Bradikinin** is the main mediator of HAE
- **Icatibant** (Firazyr®) is a selective antagonist of the bradikinin receptor B2
- Icatibant has been administered in adults at 30 mg s.c.
- The time of symptoms regression was 2,5 h in treated patients versus 4,6 h in patient treated with placebo (FAST-1)
- The time to the first symptom relief was 1,5 h in Icatibant group and 6,9 h in patients treated with tranexamic acid (FAST-2)
- No adverse effects in both trials

Cicardi *et al.* N. Engl. J. Med. 363: 532, 2010

Pharmacologic Therapy of acute attacks in HAE with Ecallantide

- Ecallantide is a recombinant peptide of 60 aa that selectively inhibits plasmatic callicrein
- Ecallantide mimics the physiological function of C1-INH
- Ecallantide (30 mg s.c.) shortens the duration of attacks (1-4 h) in patients with HAE

Cicardi *et al.* N. Engl. J. Med. 363: 523, 2010

Short term phophylaxis of hereditary angioedema (HAE)

- **C1-INH concentrate** e.v. 1 h before a high-risk situation
- **Danazole** 200 mg per os (3x die) from 5 days before to 3 days after a high-risk situation

Long term phophylaxis of hereditary angioedema (HAE)

- **Danazole** 50-200 mg/die per os monitoring liver toxicity and lipid profile

or

- **1,000 UI of C1-INH concentrate** every 3-4 days reduced the frequency of the attacks by 50%

Conclusions

- Angioedema is a heterogeneous disease
- Diagnosis of various types and forms requires a specialized team
- Diagnosis of various types and forms is necessary for therapy and prevention of attacks
- New therapeutic strategies are now available for treatment and prevention of angioedema attacks