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The role of bradykin in urticaria and angioedema, investigation and treatment

Torsten Zuberbier

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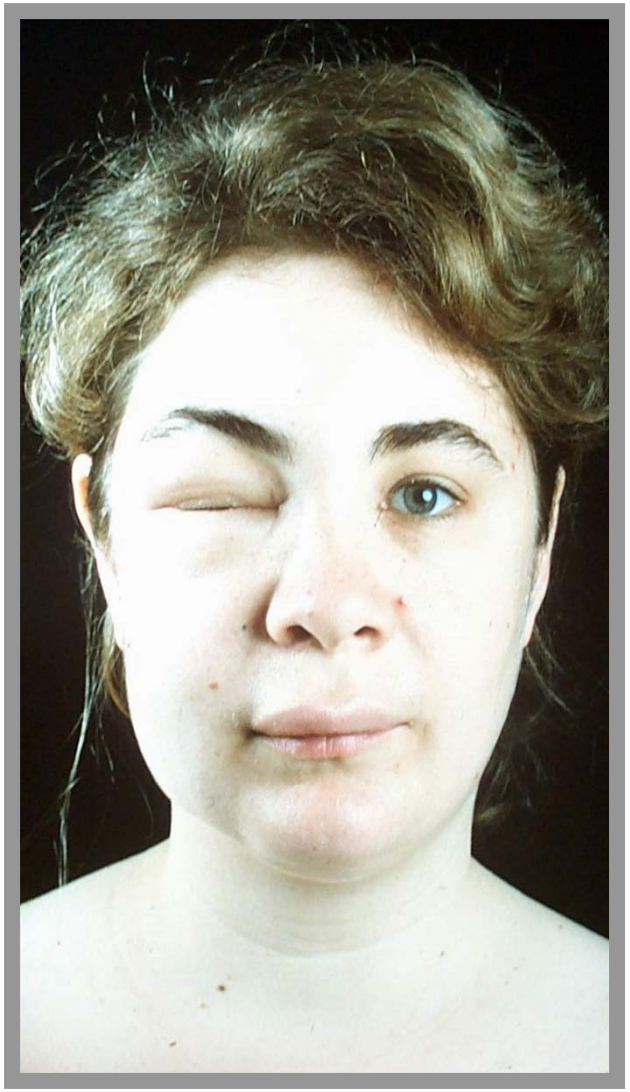

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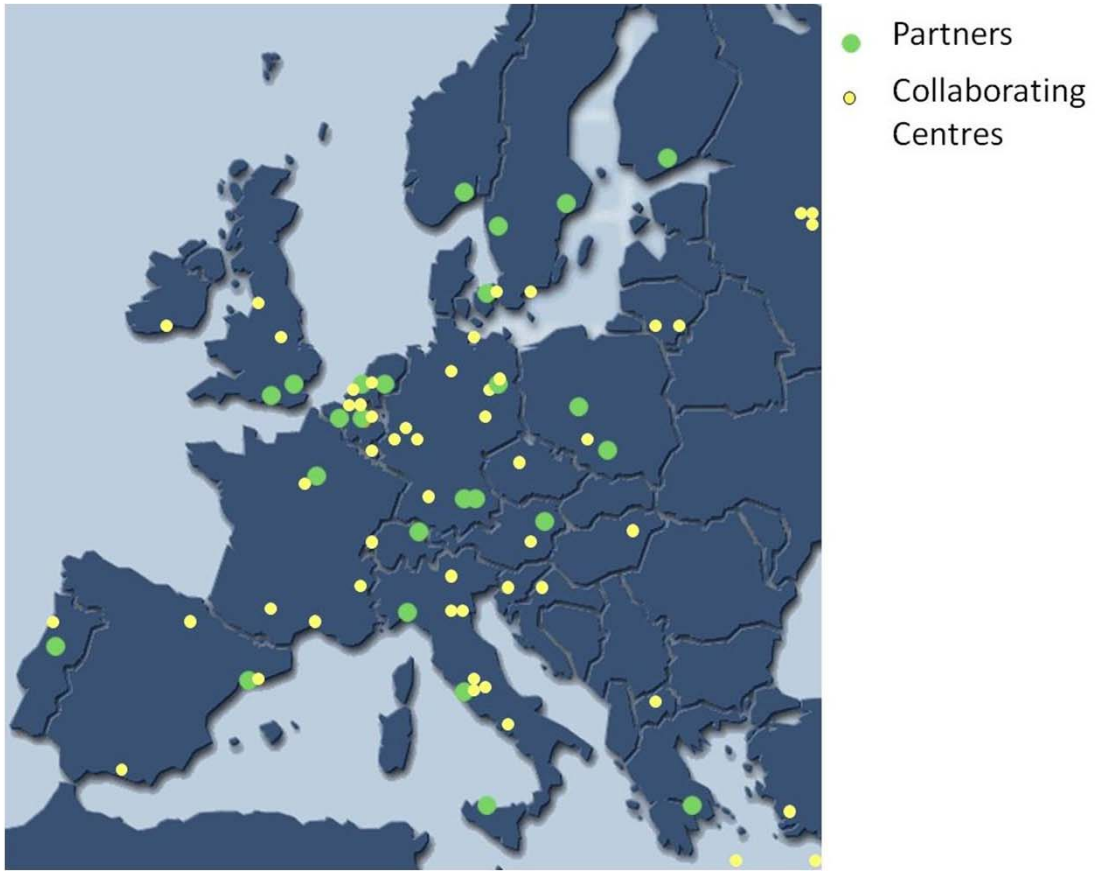

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3RD INTERNATIONAL CONSENSUS MEETING ON URTICARIA
URTICARIA 2008

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Classification

Allergy 2009: 64: 1417–1426

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Position paper

EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria

This guideline, together with its sister guideline on the management of urticaria [Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA²LEN/EDF/WAO Guideline: Management of urticaria. Allergy, 2009; **64**:1427–1443] is the result of a consensus reached during a panel discussion at the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*, a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO). Urticaria is a frequent disease. The life-time prevalence for any subtype of urticaria is approximately 20%. Chronic spontaneous urticaria and other chronic forms of urticaria do not only cause a decrease in quality of life, but also affect performance at work and school and, as such, are members of the group of severe allergic diseases. This guideline covers the definition and classification of urticaria, taking into account the recent progress in identifying its causes, eliciting factors, and pathomechanisms. In addition, it outlines evidence-based diagnostic approaches for different subtypes of urticaria. The correct management of urticaria, which is of paramount importance for patients, is very complex and is consequently covered in a separate guideline developed during the same consensus meeting. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

T. Zuberbier[1], R. Asero[2], C. Bindslev-Jensen[3], G. Walter Canonica[4], M. K. Church[1], A. Giménez-Arnau[5], C. E. H. Grattan[6], A. Kapp[7], H. F. Merk[8], B. Rogala[9], S. Saini[10], M. Sánchez-Borges[11], P. Schmid-Grendelmeier[12], H. Schünemann[13], P. Staubach[14], G. A. Vena[15], B. Wedi[7], M. Maurer[1]

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Key words: consensus; diagnosis; guideline; urticaria; wheal

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Management

Allergy 2009: 64: 1427–1443

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Position paper

EAACI/GA²LEN/EDF/WAO guideline: management of urticaria

This guideline, together with its sister guideline on the classification of urticaria (Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA²LEN/EDF/WAO Guideline: definition, classification and diagnosis of urticaria. Allergy 2009;**64**: 1417–1426), is the result of a consensus reached during a panel discussion at the Third International Consensus Meeting on Urticaria, *Urticaria 2008*, a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO). As members of the panel, the authors had prepared their suggestions regarding management of urticaria before the meeting. The draft of the guideline took into account all available evidence in the literature (including Medline and Embase searches and hand searches of abstracts at international allergy congresses in 2004–2008) and was based on the existing consensus reports of the first and the second symposia in 2000 and 2004. These suggestions were then discussed in detail among the panel members and with the over 200 international specialists of the meeting to achieve a consensus using a simple voting system where appropriate. Urticaria has a profound impact on the quality of life and effective treatment is, therefore, required. The recommended first line treatment is new generation, nonsedating H_1-antihistamines. If standard dosing is not effective, increasing the dosage up to four-fold is recommended. For patients who do not respond to a four-fold increase in dosage of nonsedating H_1-antihistamines, it is recommended that second-line therapies should be added to the antihistamine treatment. In the choice of second-line treatment, both their costs and risk/benefit profiles are most important to consider. Corticosteroids are not recommended for long-term treatment due to their unavoidable severe adverse effects. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

T. Zuberbier[1], R. Asero[2], C. Bindslev-Jensen[3], G. Walter Canonica[4], M. K. Church[1], A. M. Giménez-Arnau[5], C. E. H. Grattan[6], A. Kapp[7], M. Maurer[1], H. F. Merk[8], B. Rogala[9], S. Saini[10], M. Sánchez-Borges[11], P. Schmid-Grendelmeier[12], H. Schünemann[13], P. Staubach[14], G. A. Vena[15], B. Wedi[7]

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Key words: consensus; guideline; treatment; urticaria; wheal.

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New Guidelines

Costs	Side Effects	Therapy	Treatment Duration
		First Line	
Very low (<1 €/d)	Very low	New generation H_1-antihistamine (where available)	2 weeks
		Second Line	
Low (<5 €/d)	Very low	Increased dosage up to fourfold	1-4 weeks
		Third Line	
Low	Very low	Possible alternative nonsedating antihistamine	1-4 weeks
Low	Very low	Add on: leukotriene receptor antagonist	1-4 weeks
Medium (<10 €/d)	Medium	Systemic corticosteroid (only 3-7 days short course!)	3-7 days
		Fourth Line	
Very low	Very low	H_2-antihistamine	
Medium	Medium	Cyclosporin A	
Very low	Medium	Dapsone	
High (>10 €/d)	Very low	Omalizumab	

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Definition

Urticaria is a disease characterized by the rapid appearance of wheals and/or angioedema.

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Definition

Angioedema

- a sudden, pronounced swelling of the lower dermis and subcutis.
- It is sometimes painful rather than itching.
- There is a frequent involvement of mucous membranes and
- its resolution is slower than in wheals and can take up to 72 hours.

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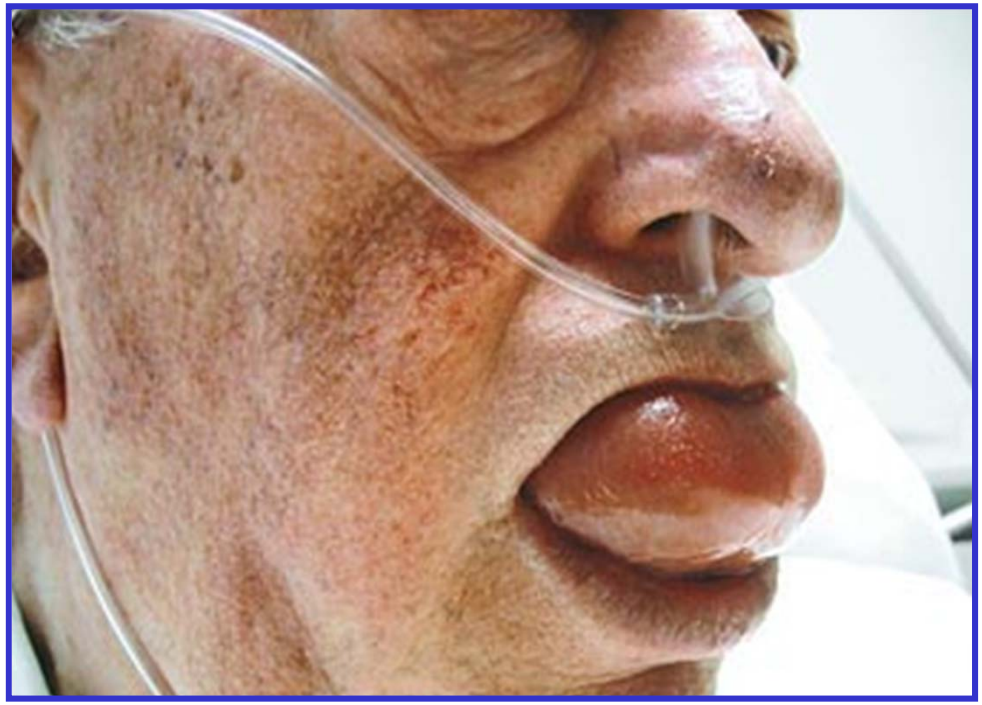
Angioedema

Swelling of skin and/or mucosa

Lasts for hours to days (usually: <72h)

Pain / Burning / Itch

(often: none of these)



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Bradykinin (BK) and Urticaria / Angioedema

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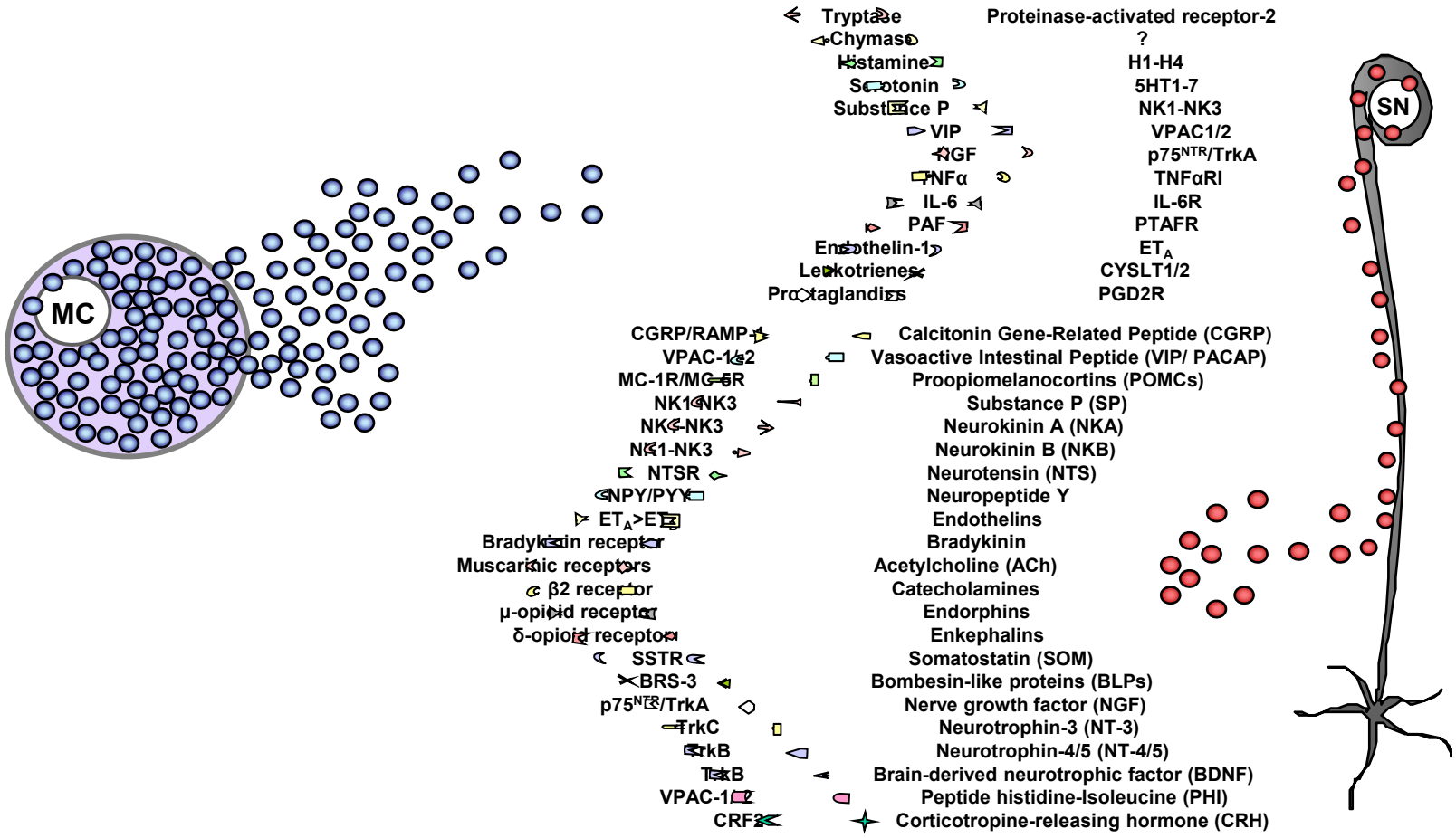
Interaction of mast cell and nerves



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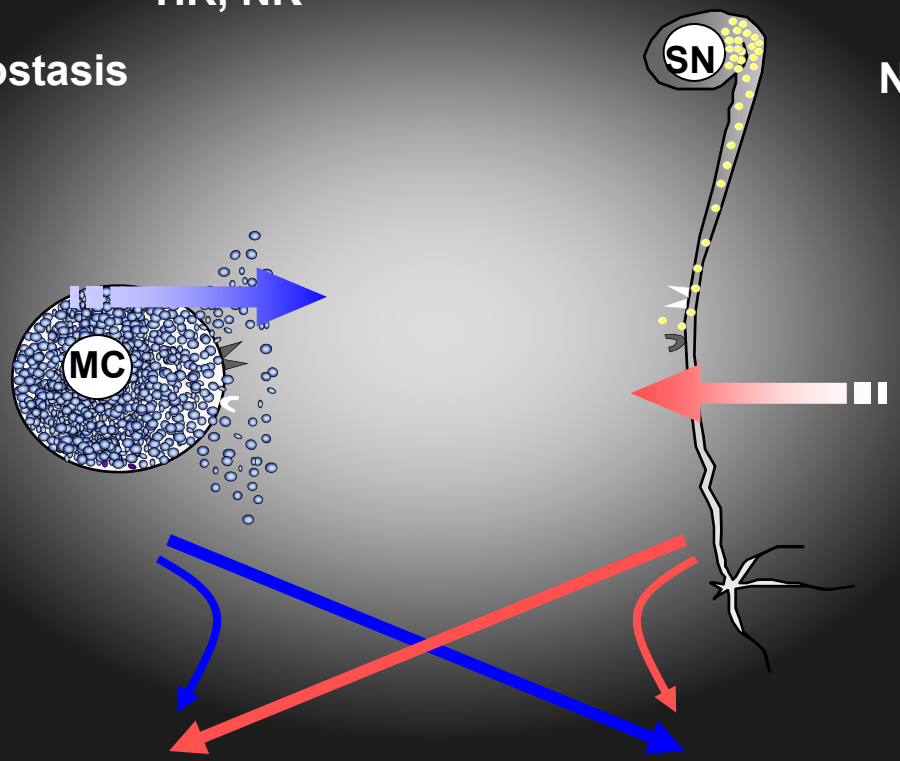
Bradykinin biology

Receptors
VR, PPAR
HR, NK

Activation
Bradykinin

Functions
‚Sentinel' & Homeostasis

Products
Neuropeptides
NGF



Physiology
No (little) proliferation
De- & Regranulation
Longevity

Growth-factors
NGF, SCF

Anatomy
Co-localization
MCs in nerves
Inervation of MCs

Inhibition
Cromoglyat

Inflammation

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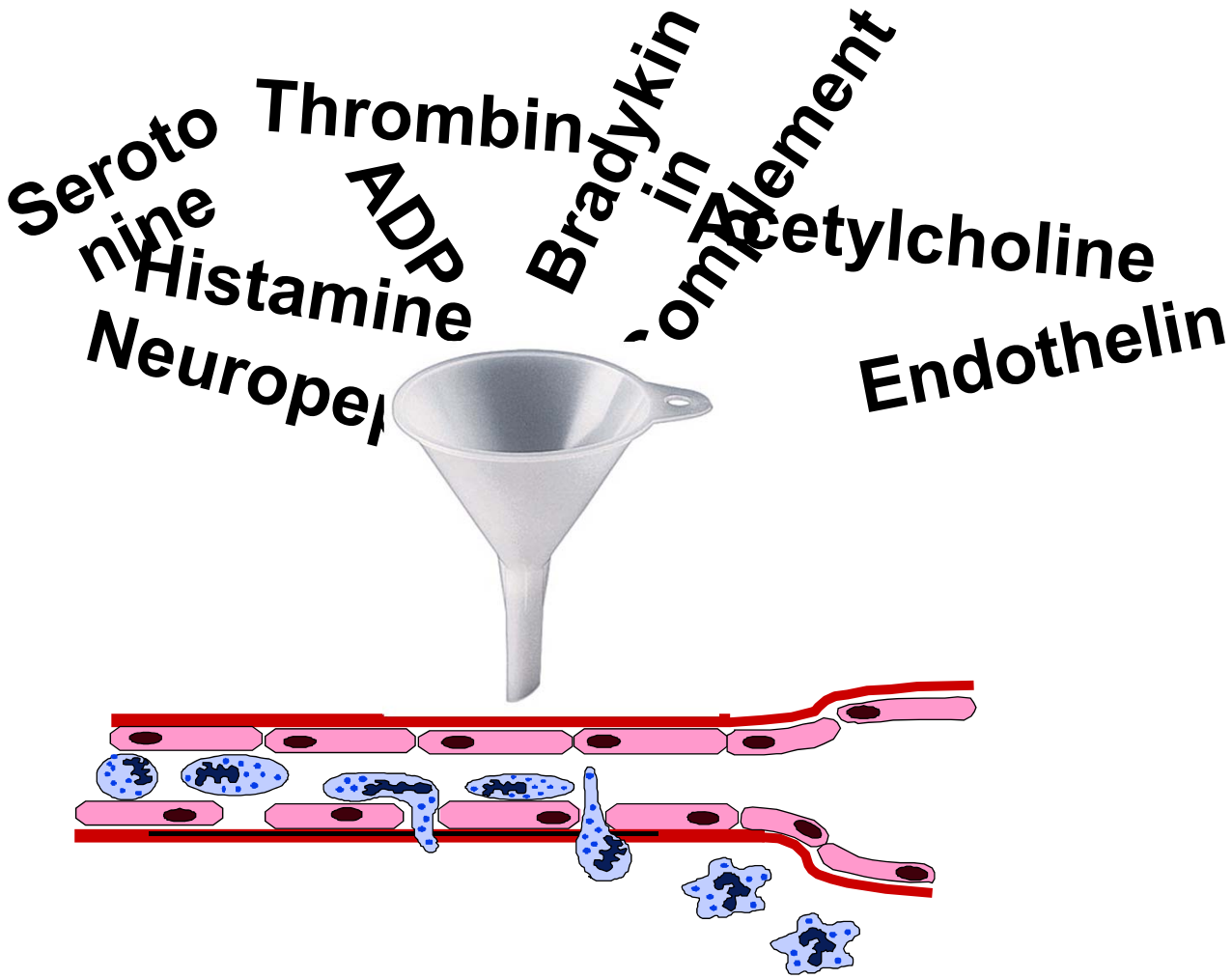
Bradykinin is an angioedema maker



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Bradykinin is an angioedema maker

Bradykinin ➤ BK2R ➤ Angioedema

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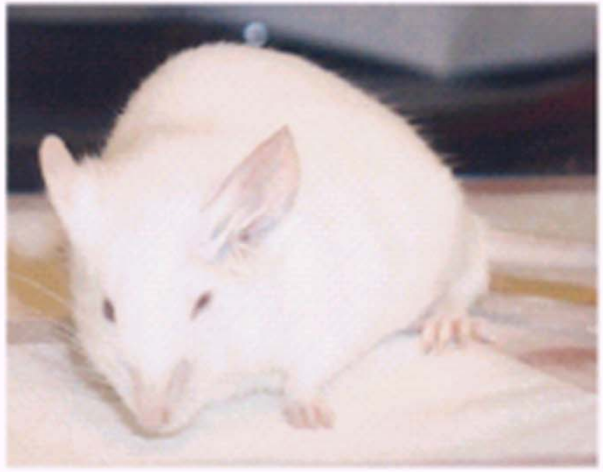
Bradykinin is an angioedema maker



Bradykin in 2 Receptor - / -

Wild-type

Han et al., *J. Clin. Invest.* 2002

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Bradykinin (BK) and Angioedema

- BK is an angioedema maker
- C1INH deficiency = BK out of control

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C1INH deficiency = Bradykinin out of control

Bradykinin ➤ BK2R ➤ Angioedema

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C1INH deficiency = Bradykinin out of control

Kininogen ➤ Bradykinin ➤ BK2R ➤ Angioedema

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C1INH deficiency = Bradykinin out of control

Kallikrein ➤ Kininogen ➤ Bradykinin ➤ BK2R ➤ Angioedema

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C1INH deficiency = Bradykinin out of control

XIIa ➤ Kallikrein ➤ Kininogen ➤ Bradykinin ➤ BK2R ➤ Angioedema

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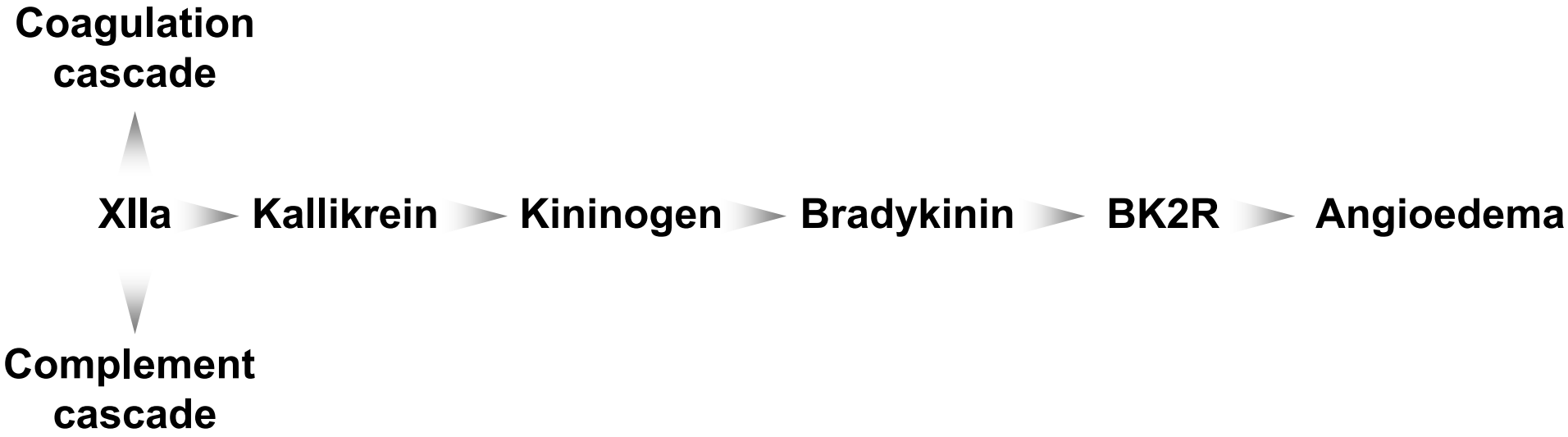
C1INH deficiency = Bradykinin out of control



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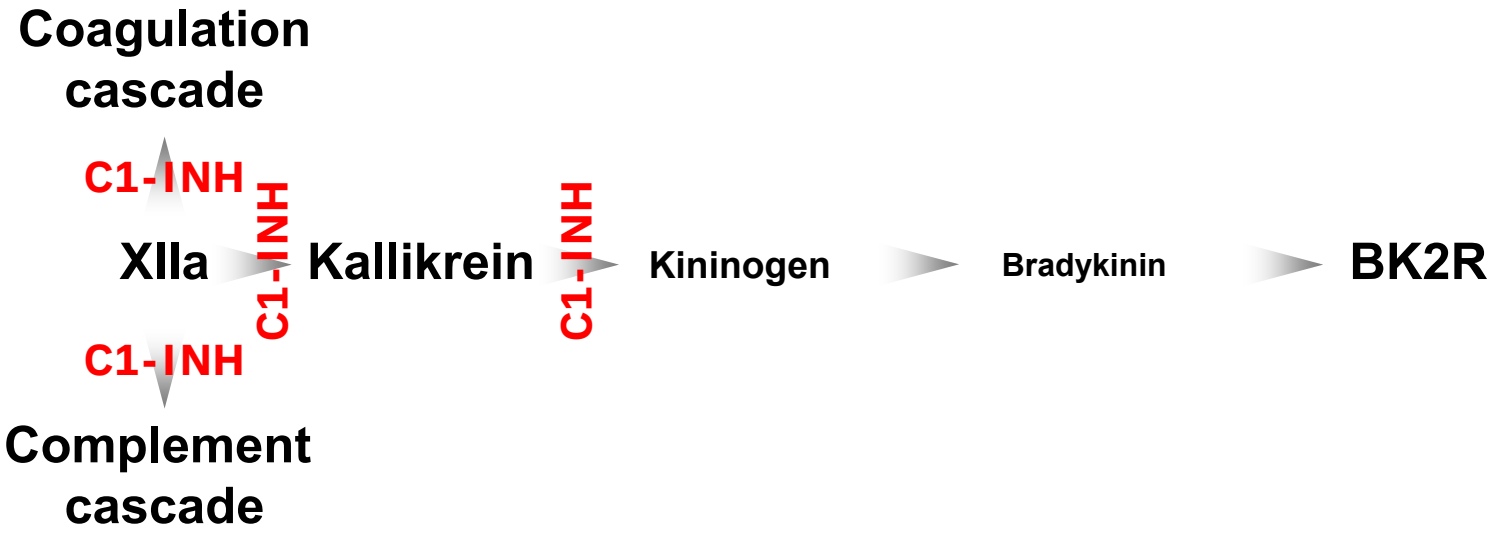
C1INH deficiency = Bradykinin out of control



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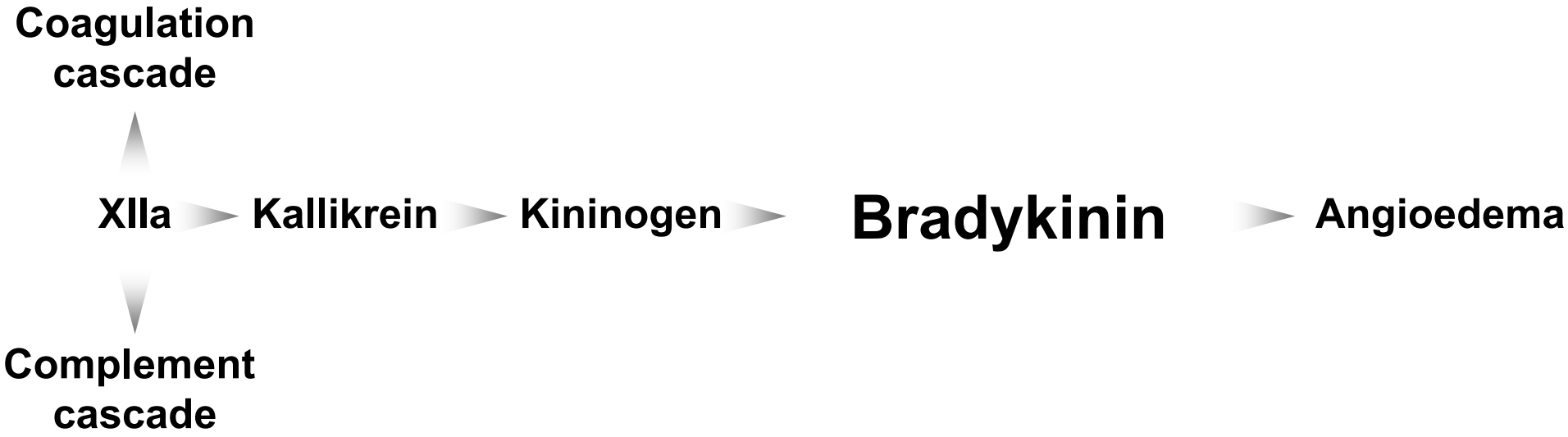
C1INH deficiency = Bradykinin out of control



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Bradykinin out of control = Angioedema

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Bradykinin out of control = Angioedema

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Bradykinin out of control = Angioedema

Coagulation cascade

XIIa → Kallikrein → Kininogen → Bradykinin → BK2R → Angioedema

Complement cascade

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Bradykinin (BK) and Angioedema

- BK is an angioedema maker
- C1INH deficiency = BK out of control
- BK is increased in angioedema

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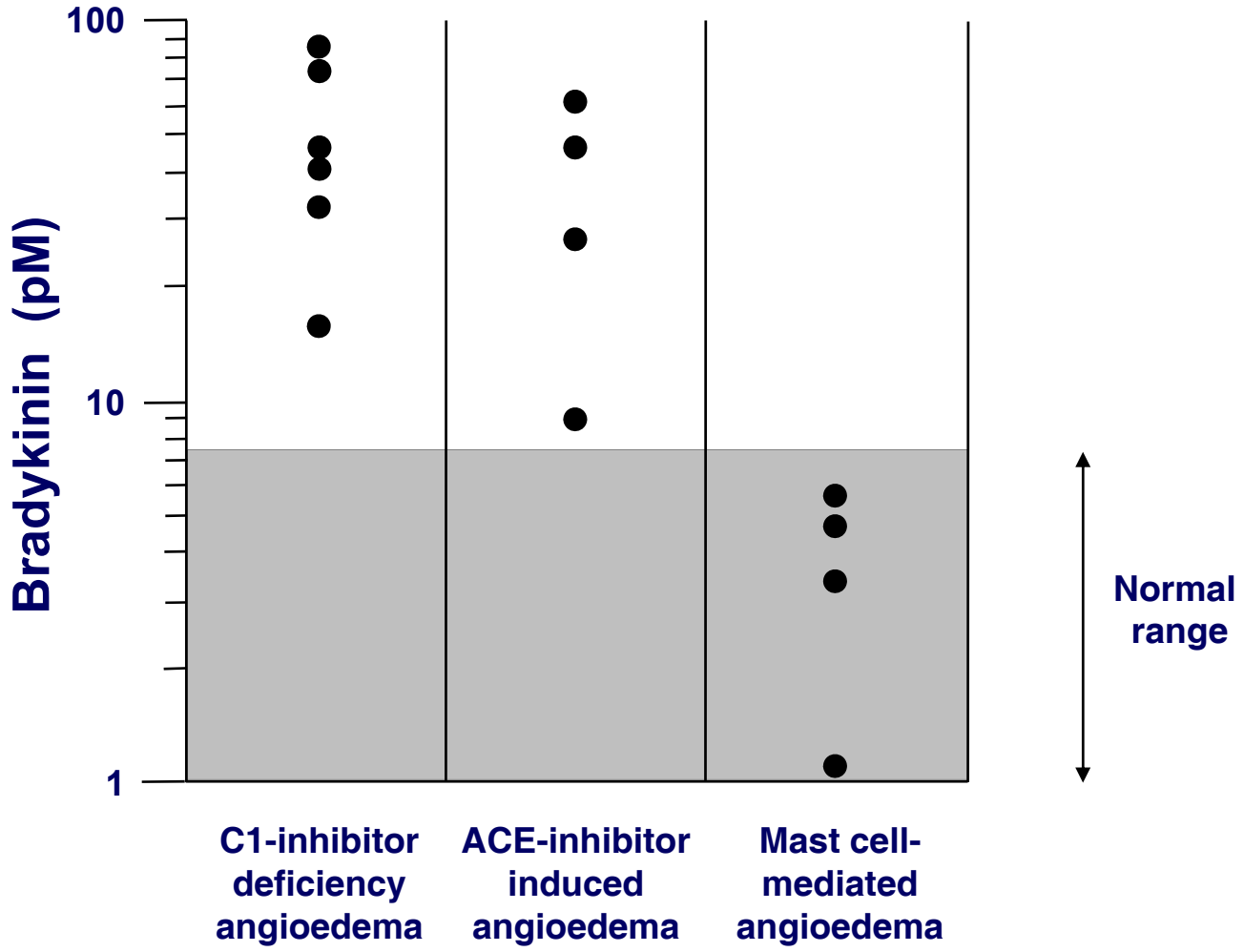
Bradykinin is increased in angioedema



Nussberger et al., *N. Engl. J. Med.* 2002

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When to consider HAE

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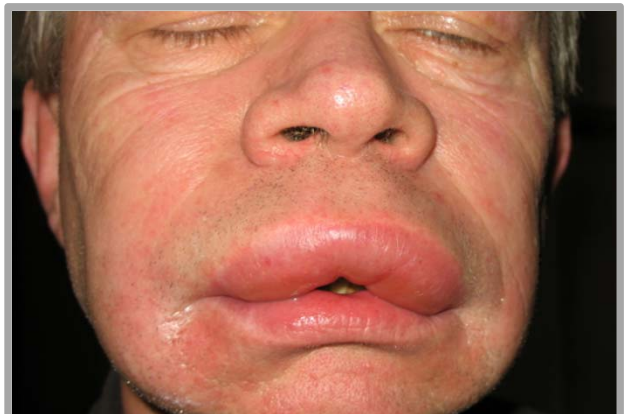

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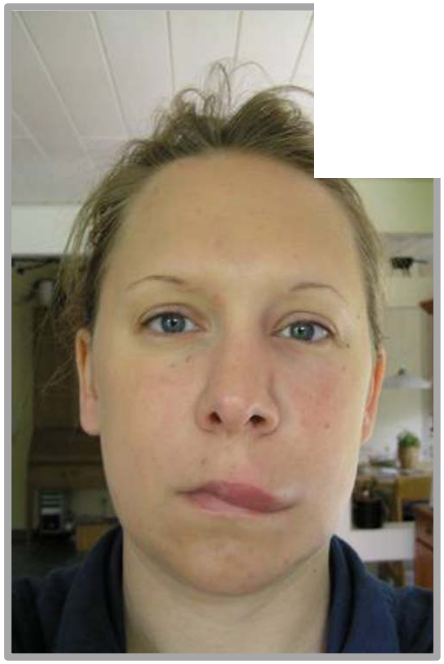

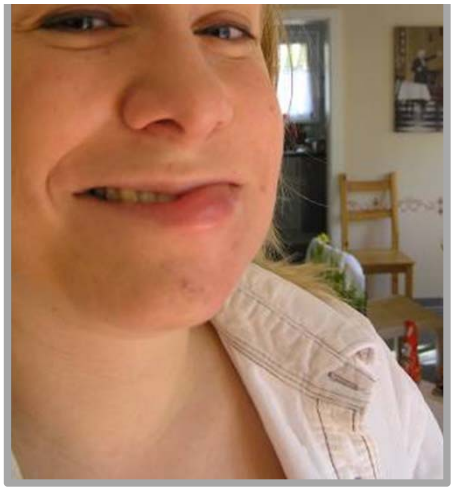

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“Pseudo-angioedema”

Lymphedema

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“Pseudo-angioedema”

Erysipelas

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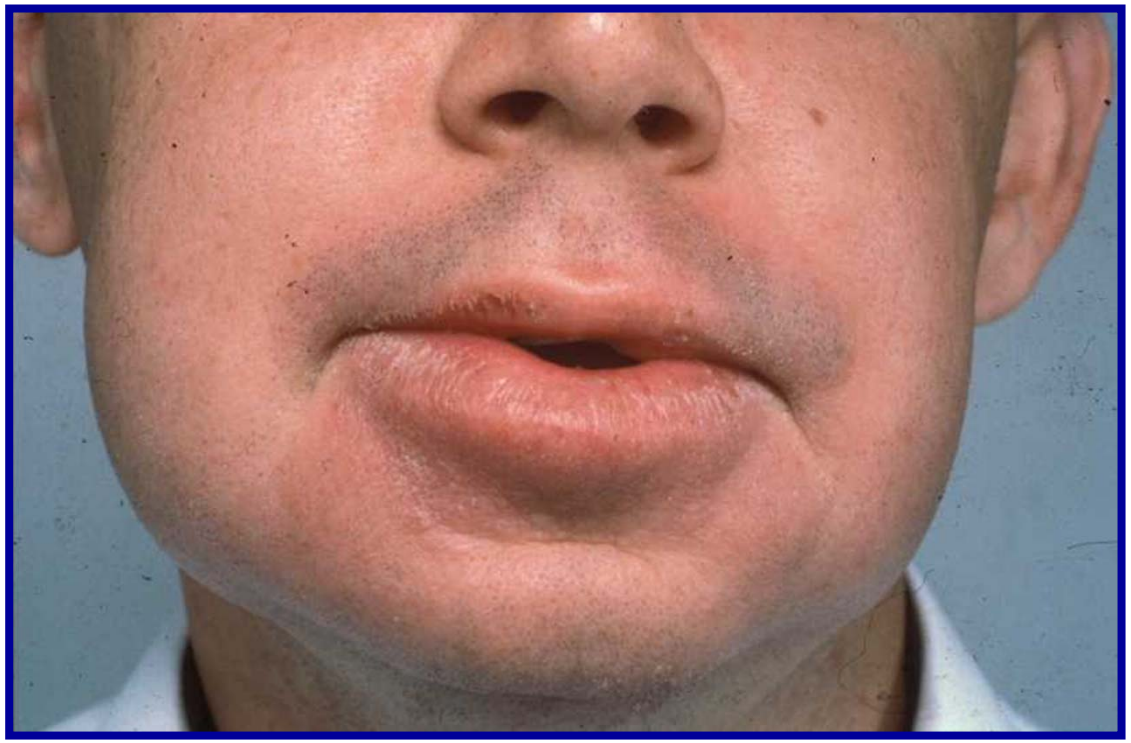

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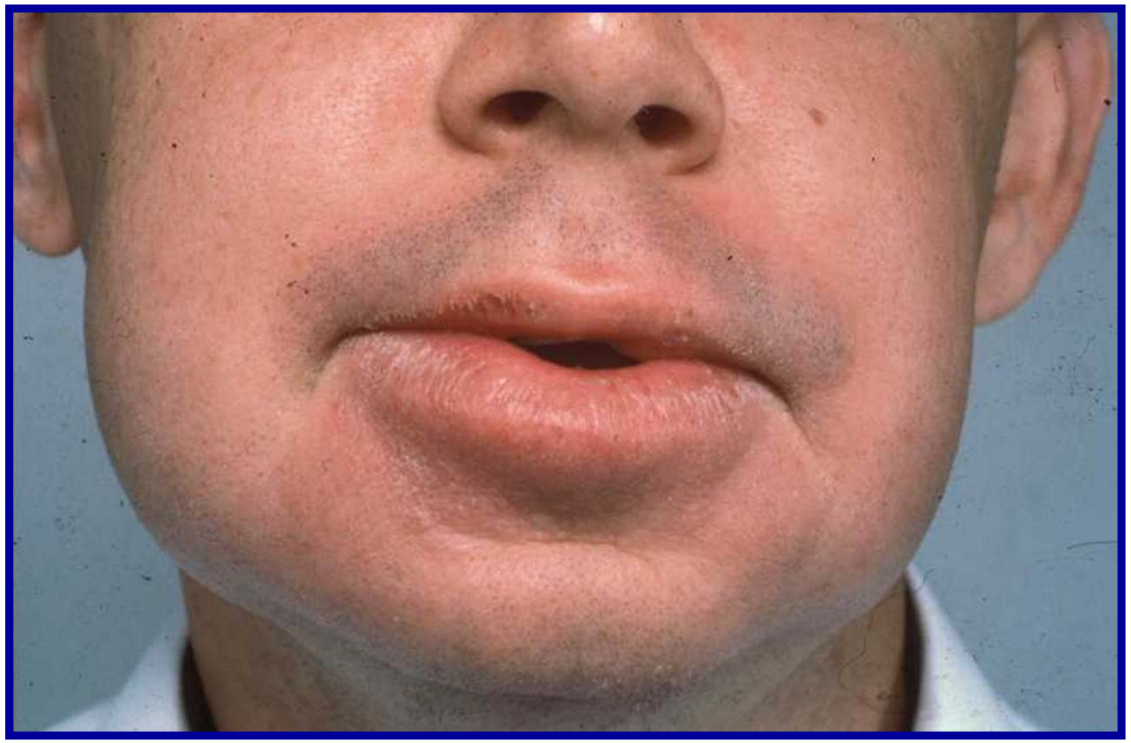
“Pseudo-angioedema”



M. Crohn

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“Pseudo-angioedema”

Dermatomyositis

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“Pseudo-angioedema”

Allergic contact dermatitis

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“Pseudo-angioedema”

M. Melkersson-Rosenthal

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“Pseudo-angioedema”

Lupus erythematosus

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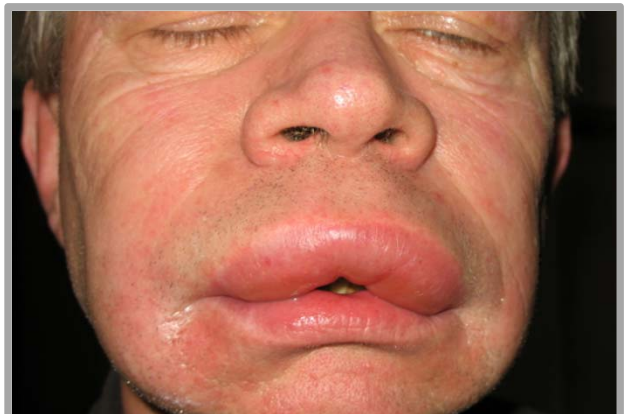
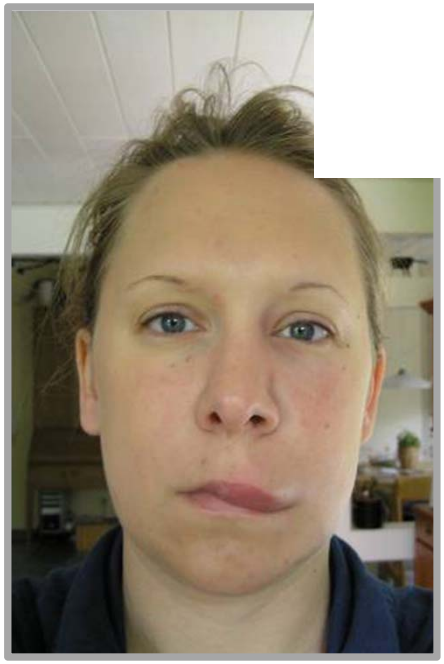
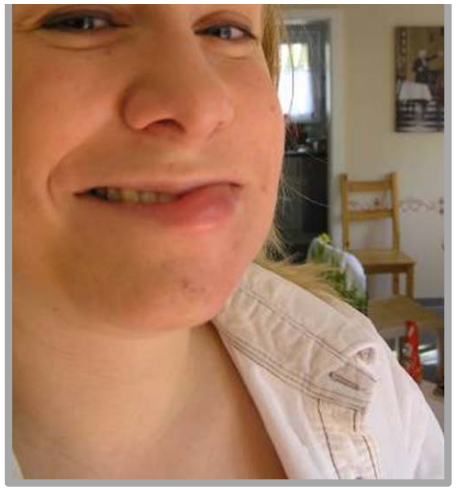


Angioedema





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Angioedema= sudden onset and < 72h duration

Mast cell mediator-mediated (With wheals[1])	**Bradykinin-mediated** (Without wheals[2])
Chronic spontaneous urticaria Autoreactive Infection Intolerance Other causes Unidentified cause Physical urticaria Other urticaria	Hereditary angioedema Type 1 (C1-Inhibitor *concentration* low) Type 2 (C1-Inhibitor *activity* low) Type 3 (related to factor XII mutation) Non-hereditary angioedema Acquired angioedema Drug induced (e.g. ACE inhibitor) Idiopathic angioedema

[1]Some patients with histamine-mediated angioedema do not exhibit wheals

[2]In very rare cases patients with bradykinin-mediated angioedema also have urticaria and therefore wheals

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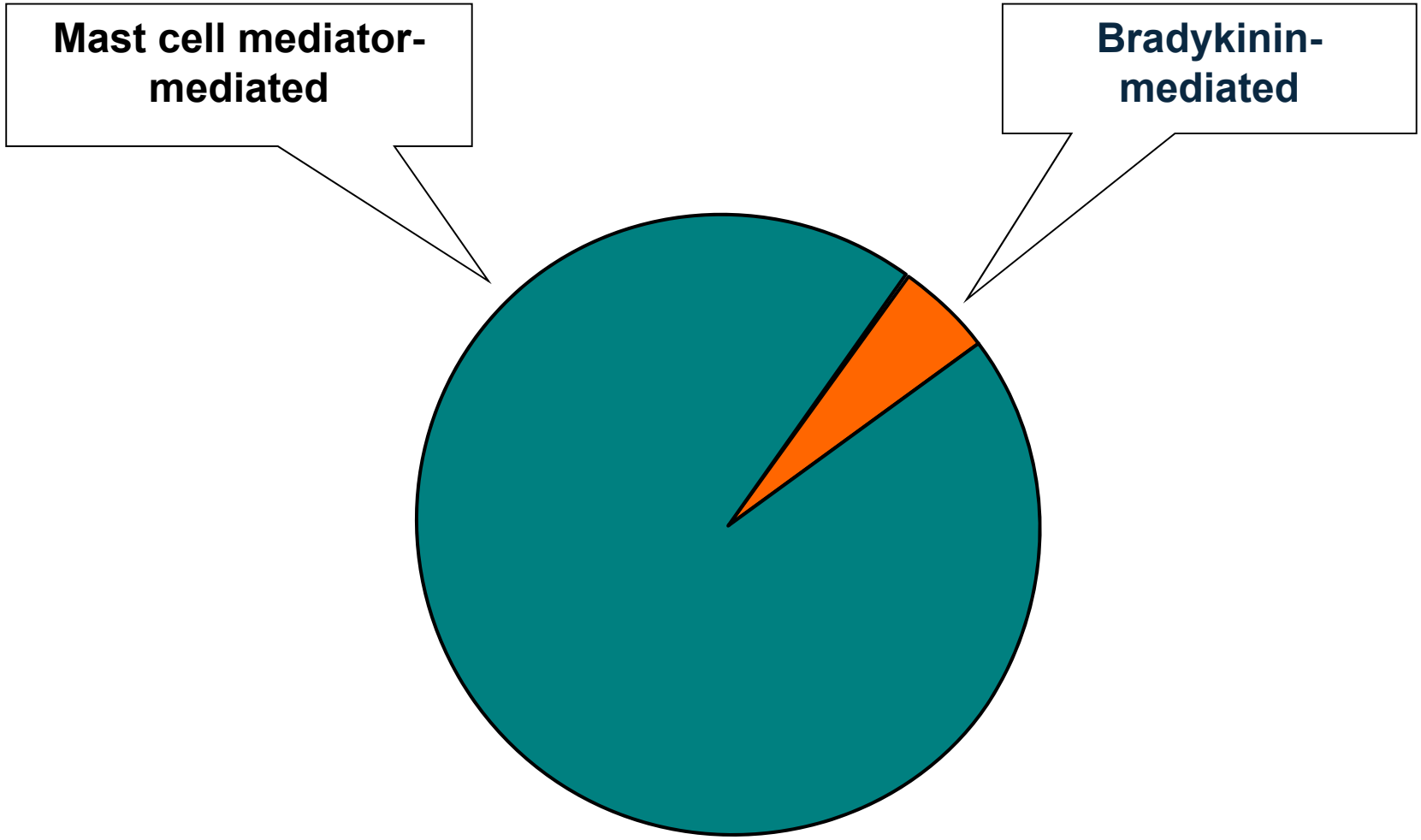
Distribution of Angioedema



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When to consider HAE

- Early onset

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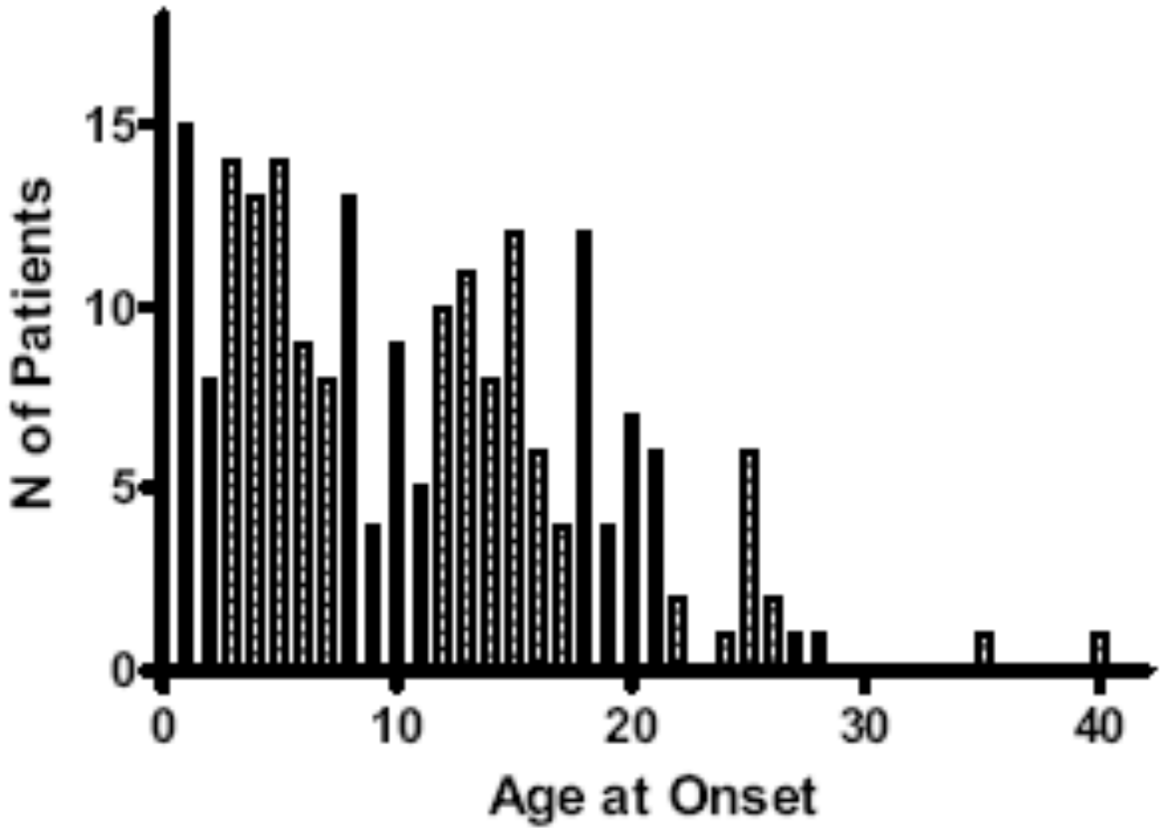

Figure 1 Age at onset of the clinical symptoms in 209 patients with hereditary angioedema due to C1 inhibitor deficiency.

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When to consider HAE

- Early onset
- Family history

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When to consider HAE

- Early onset
- Family history
- No wheals

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When to consider HAE

- Early onset
- Family history
- No wheals
- Prodromi

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Characteristics

- The disease may not only affect the skin, gastrointestinal tract, and larynx, but also various other organs.
- On average, women have a more severe course of the disease than men.
- Patients with early onset of clinical symptoms are affected more severely than those with late onset.

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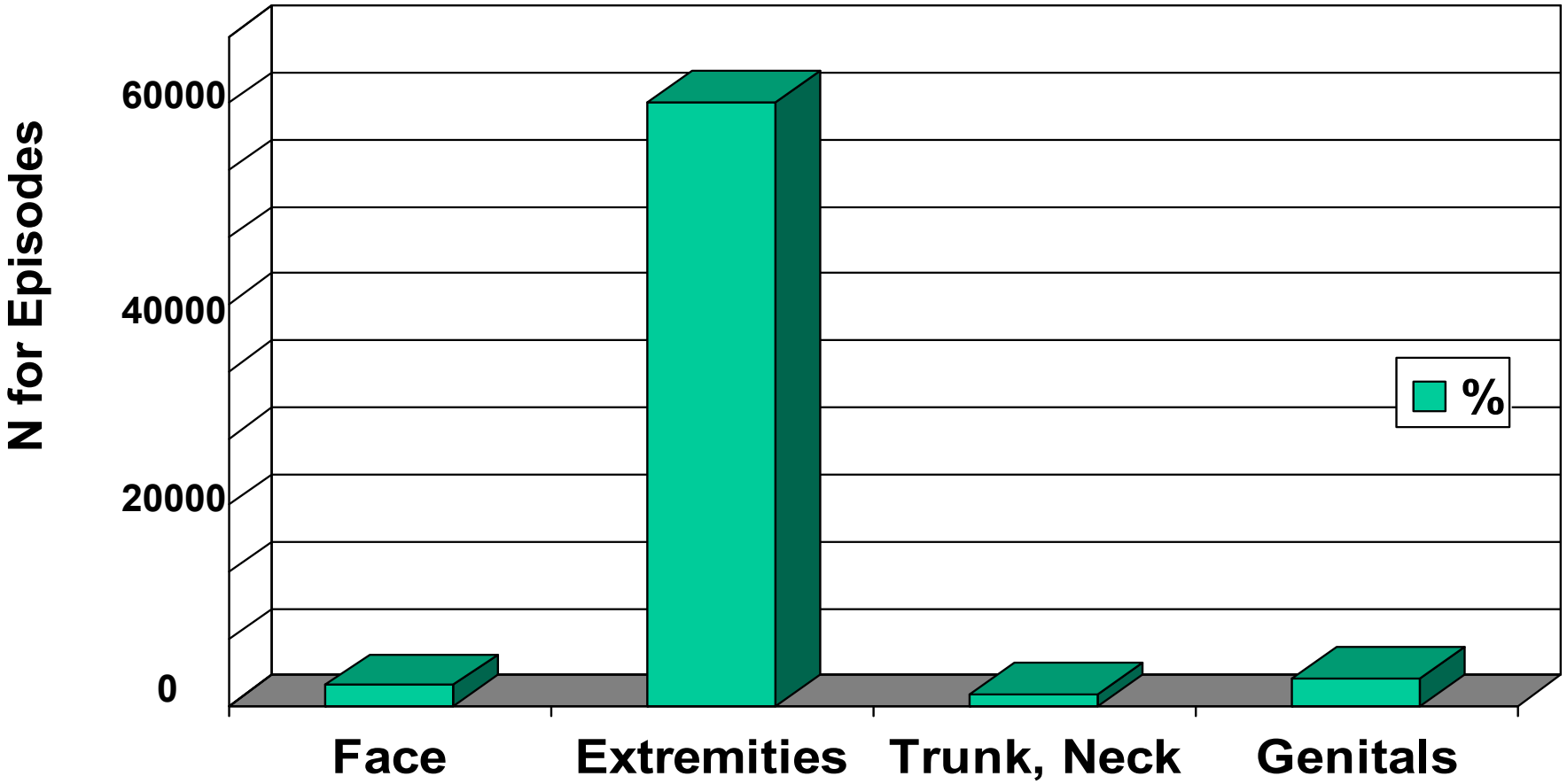
Per-Episodes Analysis



Percentage based on n=131,110 episodes; column percents do not add up to 100% due to edema episodes in other organs

modified from sourse: Bork K, Meng G, Staubach P, Hardt J

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Per-Episodes Analysis

Percentage based on n=131,110 episodes; other comprise the columns Larynx to Esophagus from A

modified from sourse: Bork K, Meng G, Staubach P, Hardt J

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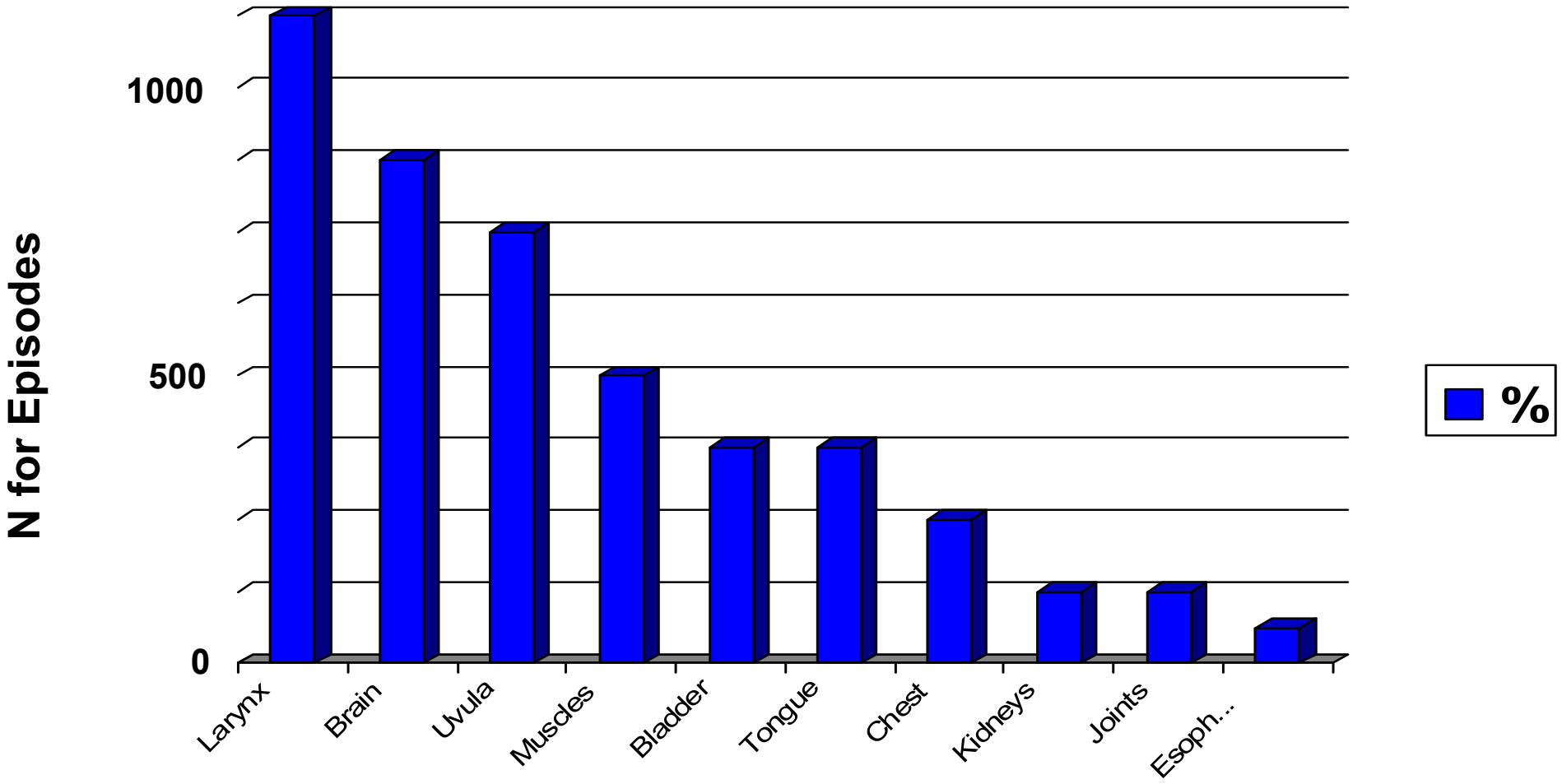

modified from sourse: Bork K, Meng G, Staubach P, Hardt J

Percentage based on n=131,110 episodes

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How long do HAE patients have symptoms before being diagnosed?

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How long do HAE patients have symptoms before being diagnosed?

13.1 years!

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Approximately 30% of undiagnosed patients with abdominal attacks undergo unnecessary surgery!

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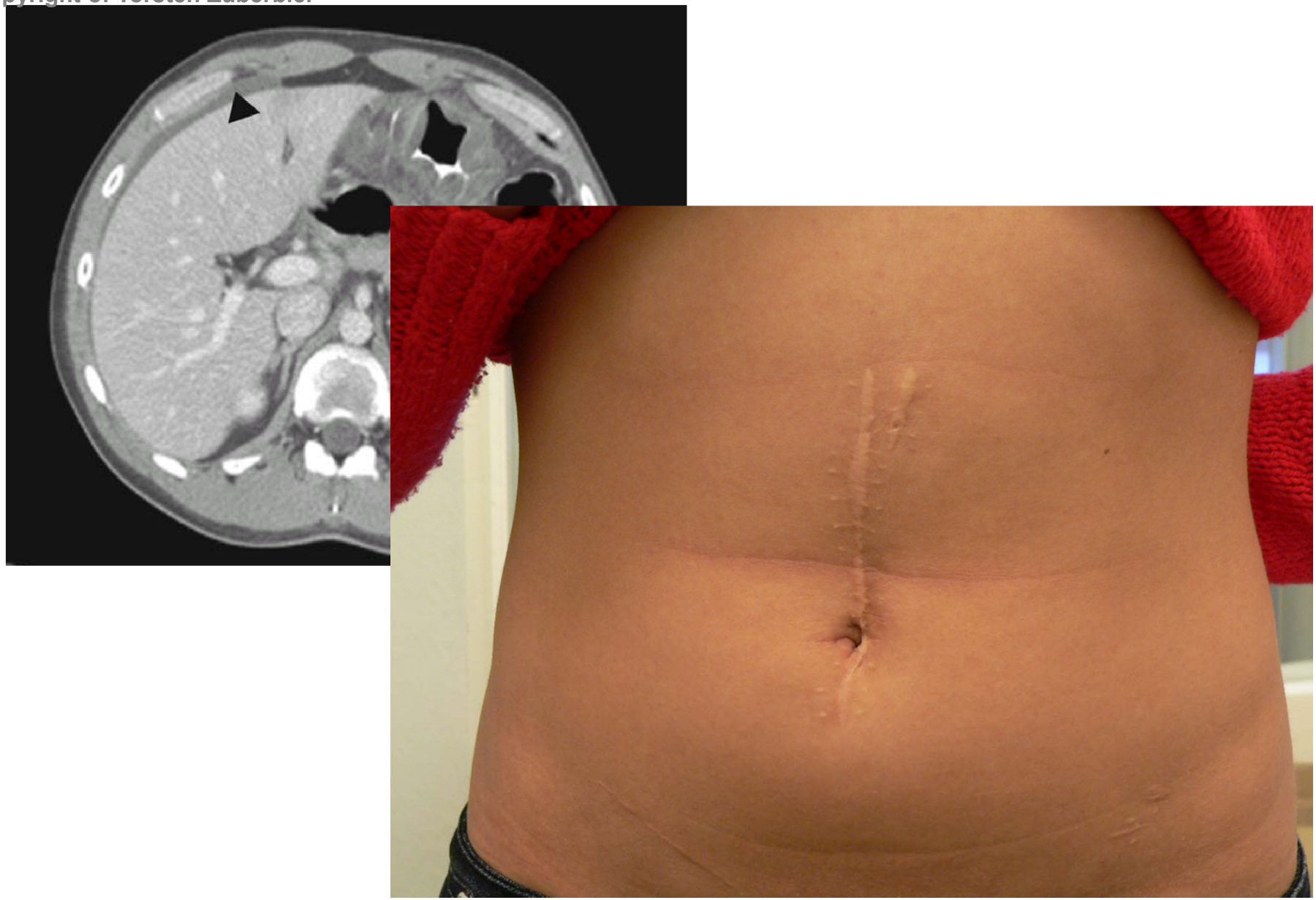

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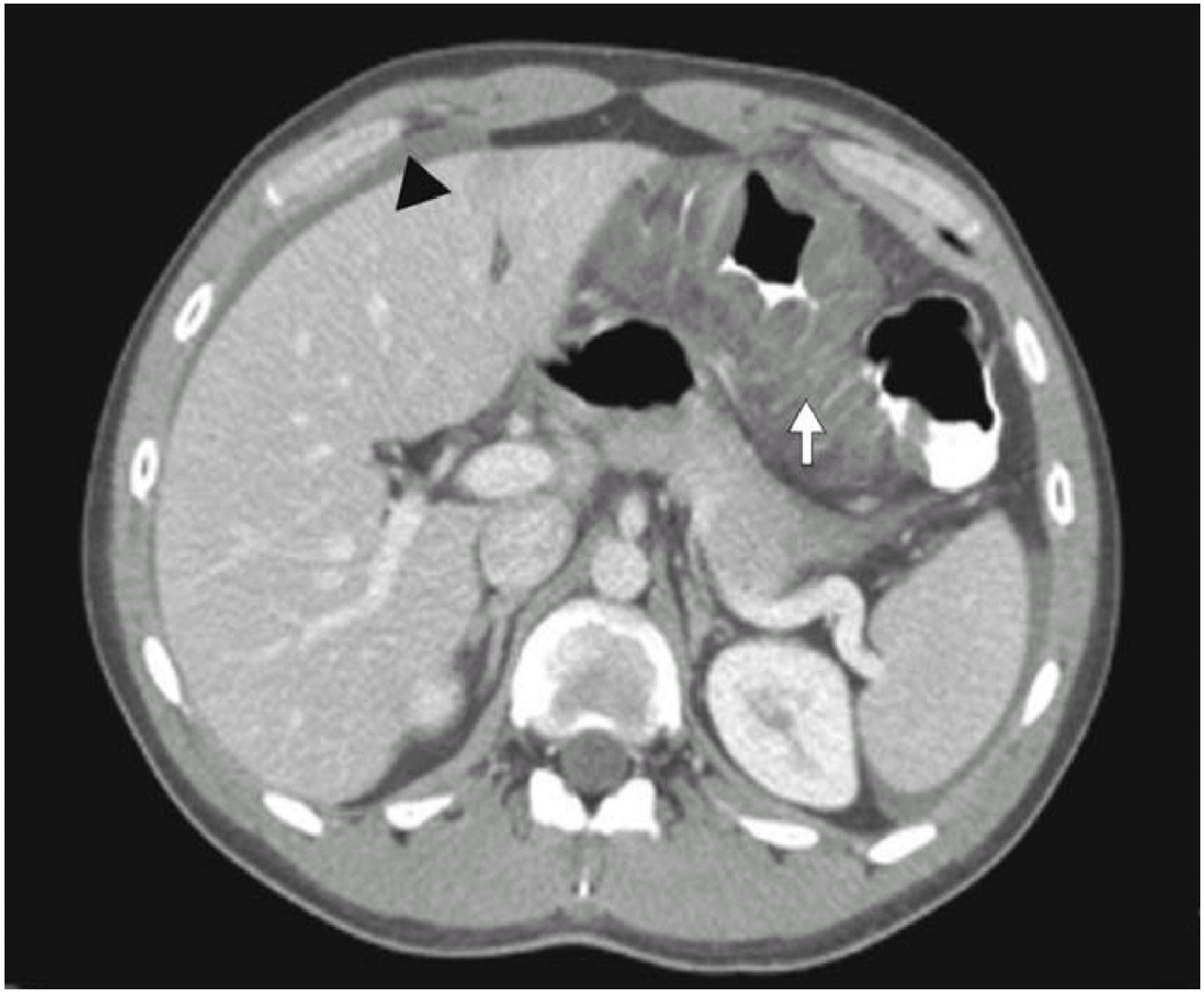

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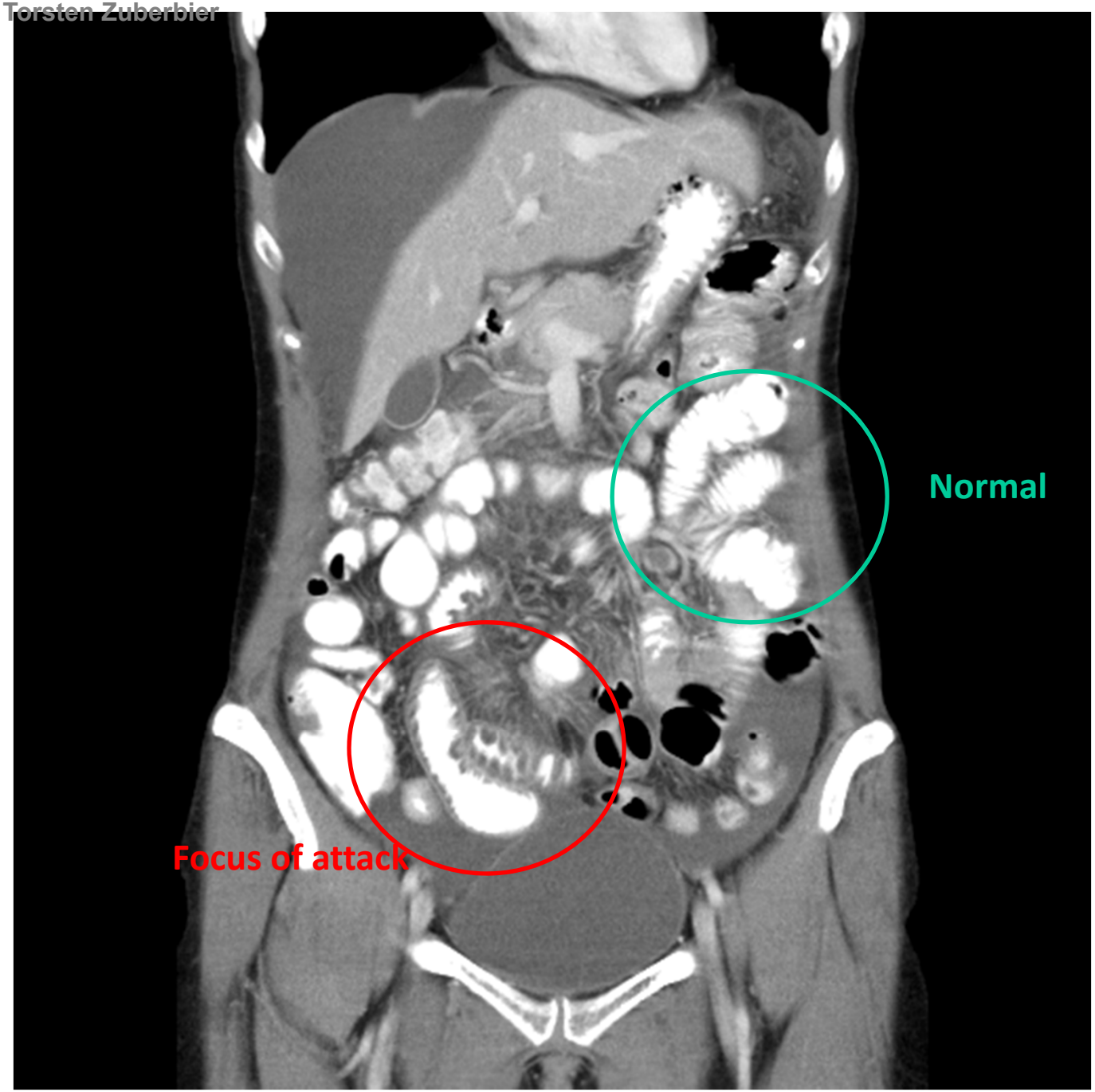

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Asphyxiation by laryngeal edema in patients with hereditary angioedema

Family	HAE Patients	Deaths	Age at death
1	7	2	9, 65
2	2	1	23
3	2	1	52
4	6	2	27, 42
5	7	2	22. 39
6	5	1	55
7	6	1	40
8	4	2	39, 42
9	6	1	54
10	6	1	68
11	4	1	27
12	8	3	4wks, 37, 53
13	4	1	43
14	10	2	35, 42
15	5	3	28, 28, 43
	82	**24**	**4wks – 68y**

Borket al Mayo Clinic Proc 2000; 75: 349354

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Diagnosis

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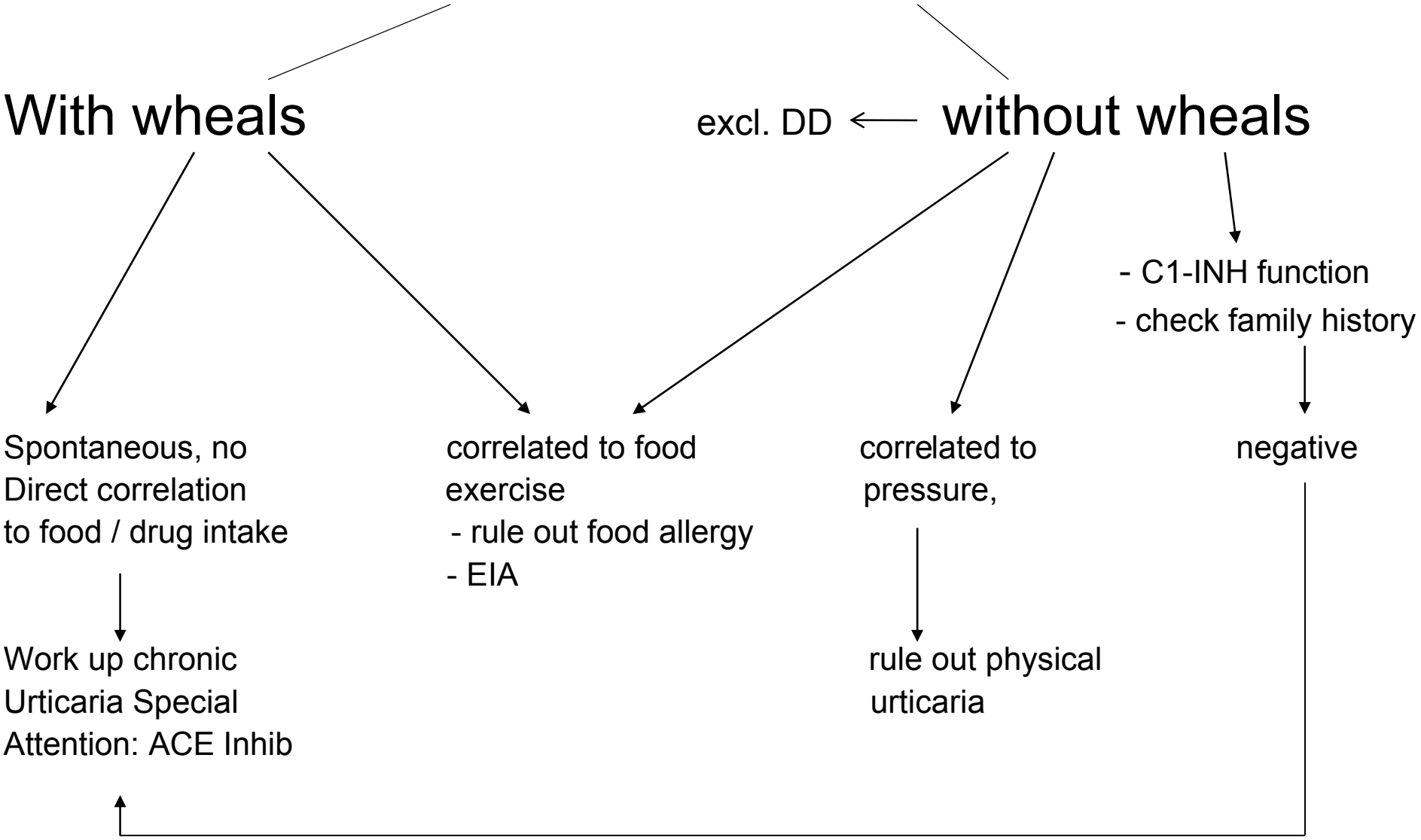
work up Angioedema



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How to diagnose HAE

- History
- (Phys. examination / Imaging)
- Lab

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C1-INH Function

C1-INH Level

C4 Level

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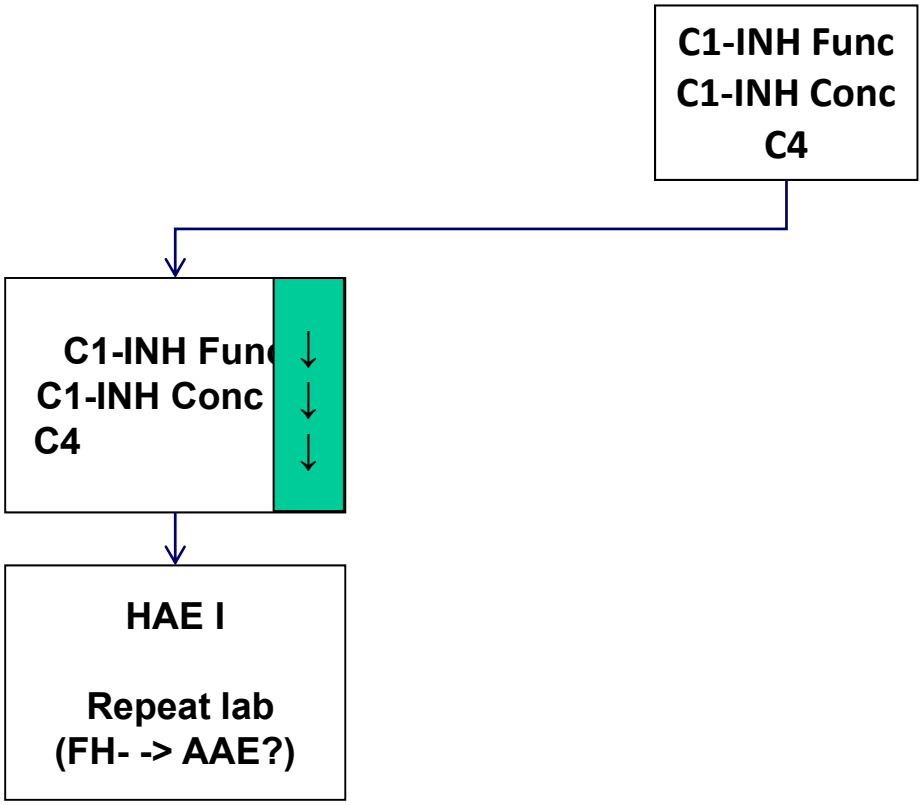

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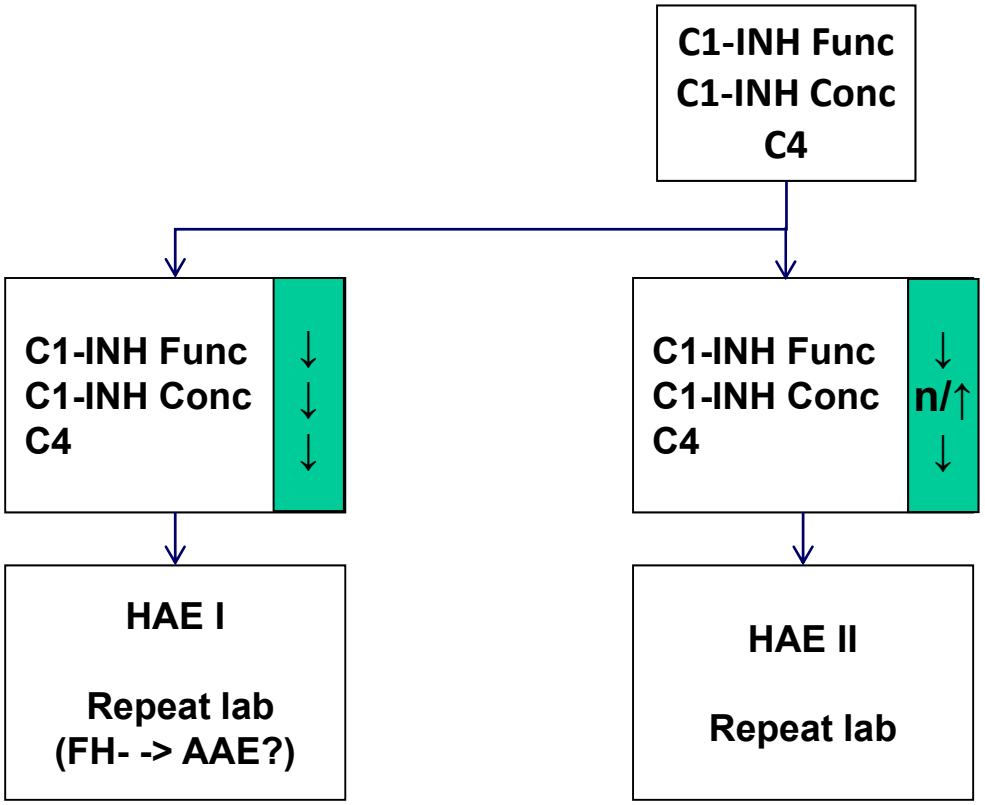

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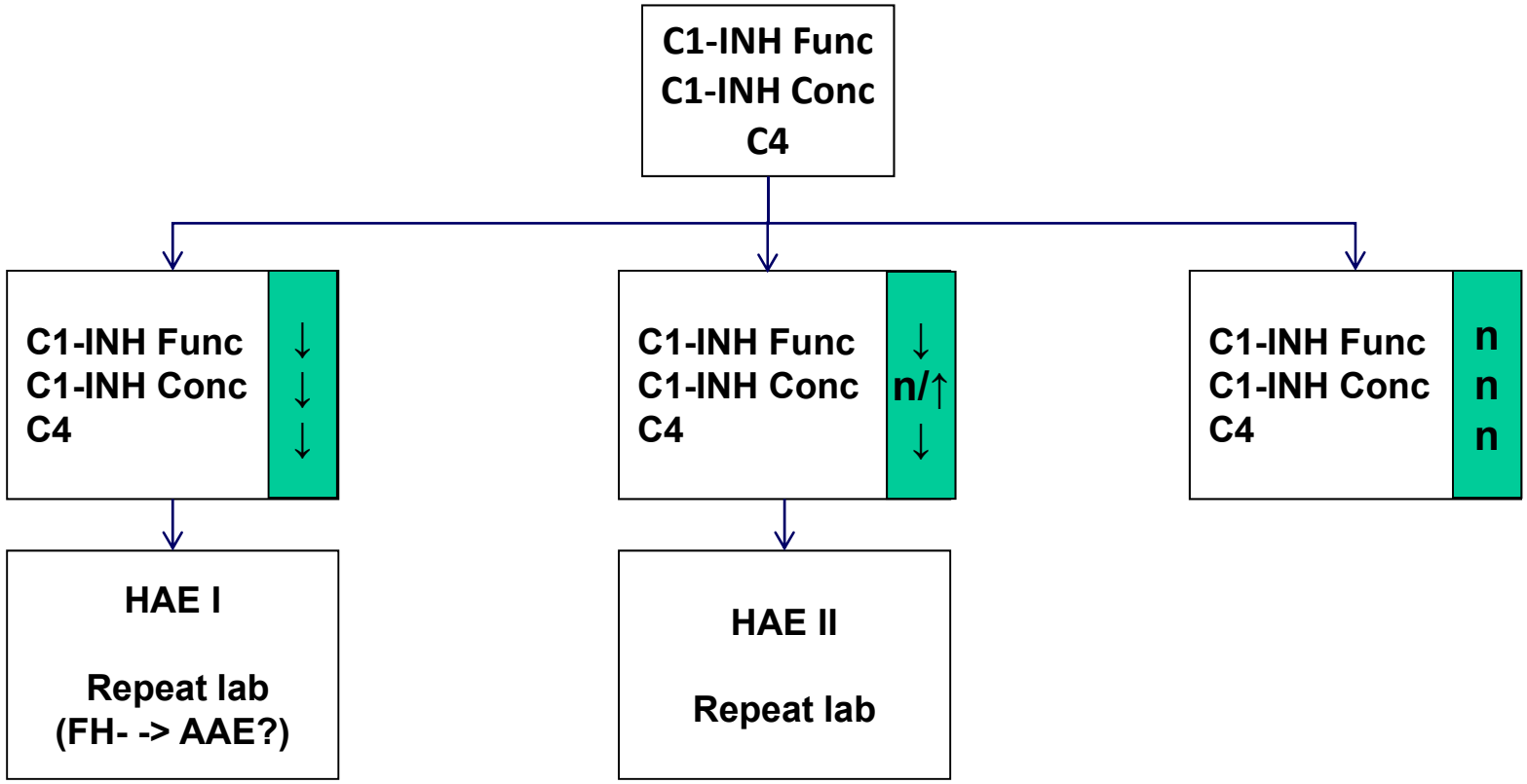

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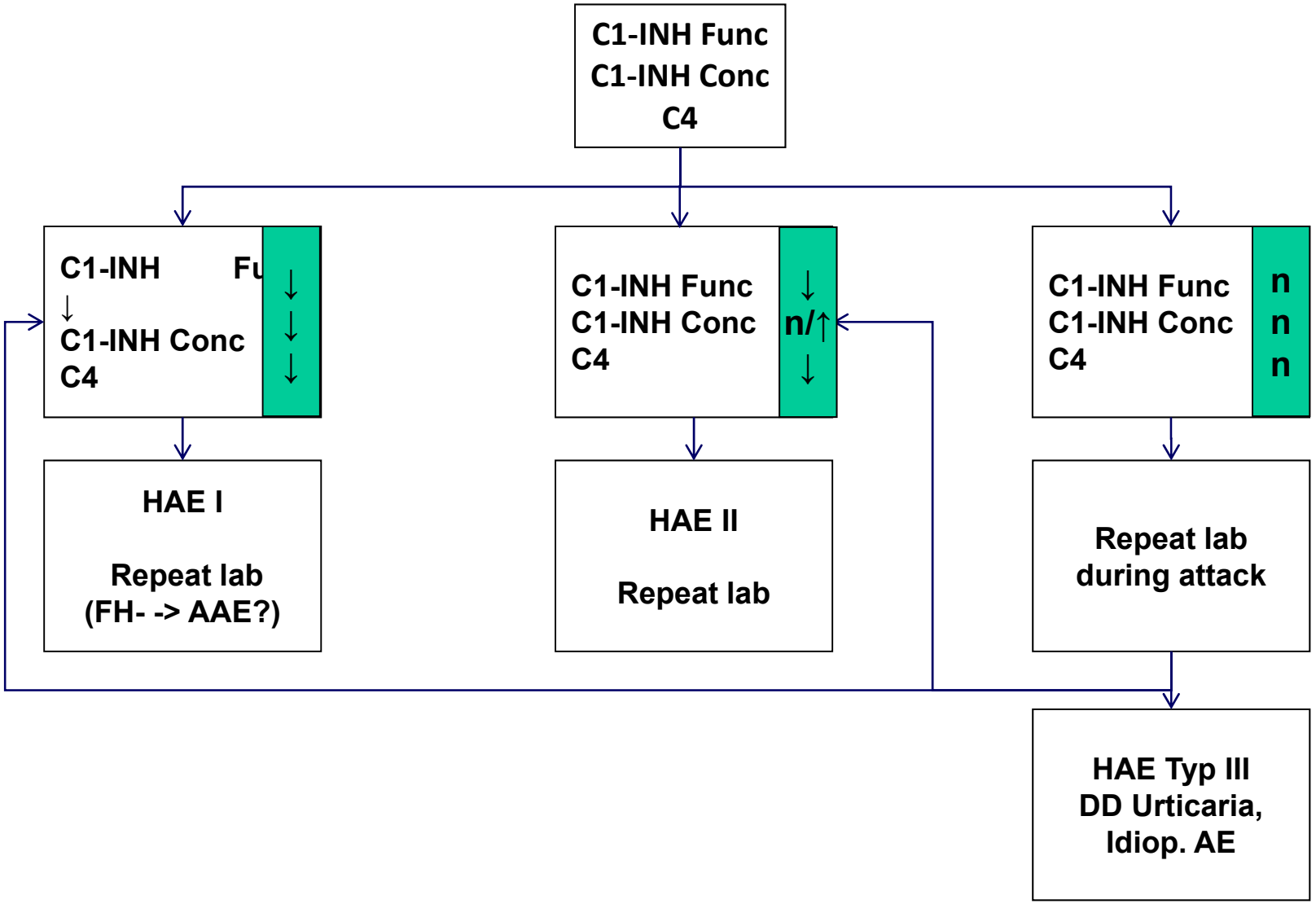

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Angioedema

Mast cell mediator-mediated (With wheals[1])	**Bradykinin-mediated** (Without wheals[2])
Chronic spontaneous urticaria Autoreactive Infection Intolerance Other causes Unidentified cause Physical urticaria Other urticaria	Hereditary angioedema Type 1 (C1-Inhibitor *concentration* low) Type 2 (C1-Inhibitor *activity* low) Type 3 (related to factor XII mutation) Non-hereditary angioedema Acquired angioedema Drug induced (e.g. ACE inhibitor) Idiopathic angioedema

[1]Some patients with histamine-mediated angioedema do not exhibit wheals

[2]In very rare cases patients with bradykinin-mediated angioedema also have urticaria and therefore wheals

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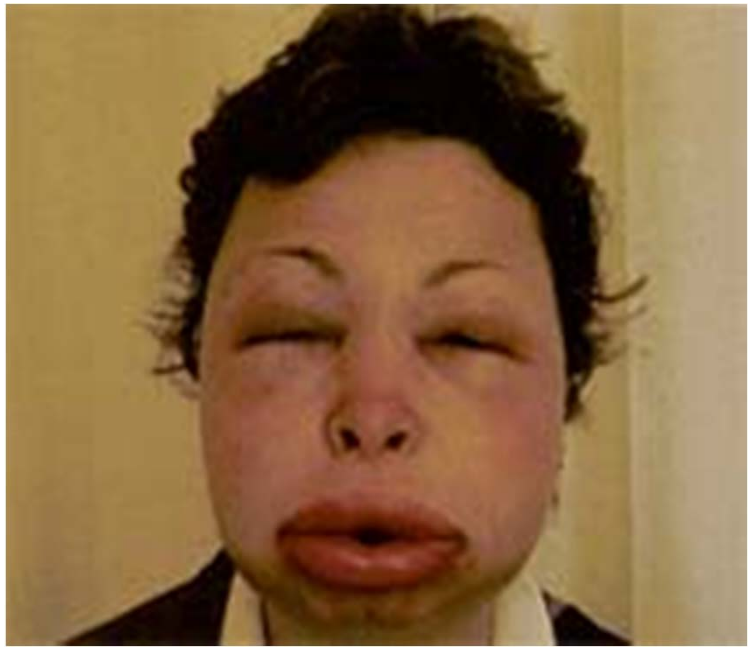

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Therapy

Bradykinin-driven angioedema (without wheals in history)
Acquired Angioedema Acquired C1-inhibitor-deficiency (Auto-AB against C1-INH, activation of complement system) RAAS-Inhibitor-inducede angioedema (e.g. by ACE-inhibitors)

ACE Inhibitor Induced

Diagnosis and treatment: omission

AT 1- antagonists often tolerated

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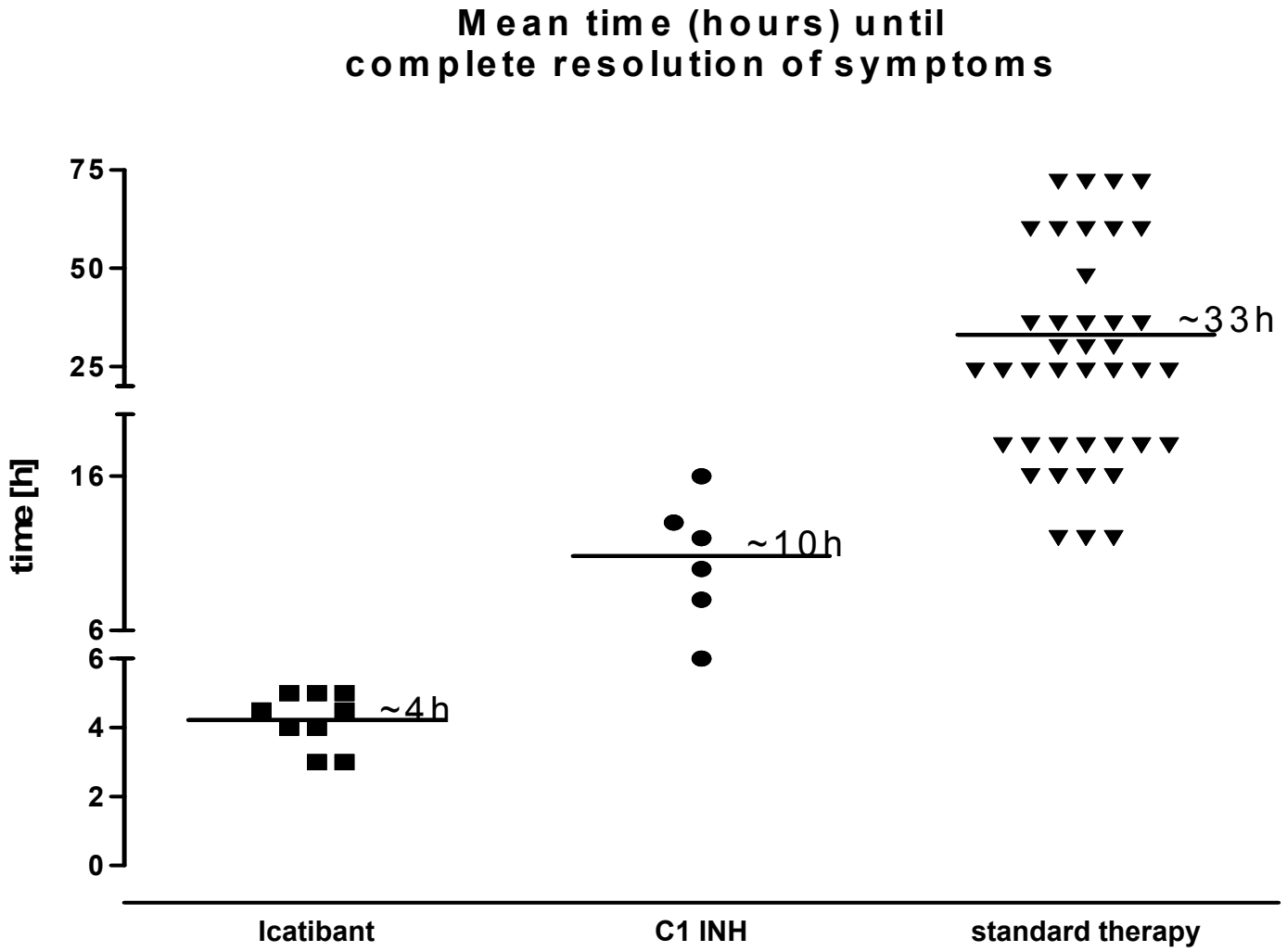
ACEinhibitor angioedema treated with icatibant



Bas et al., *unpublished data*

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Hereditary and acquired angioedema treatment

- Danazol
- C1 INH concentrate (Berinert®)
- Tranexamic acid
- Icatibant
- check for neoplasia in acquired forms

Adrenaline, antihistamines and/or glucocorticoids are not effective

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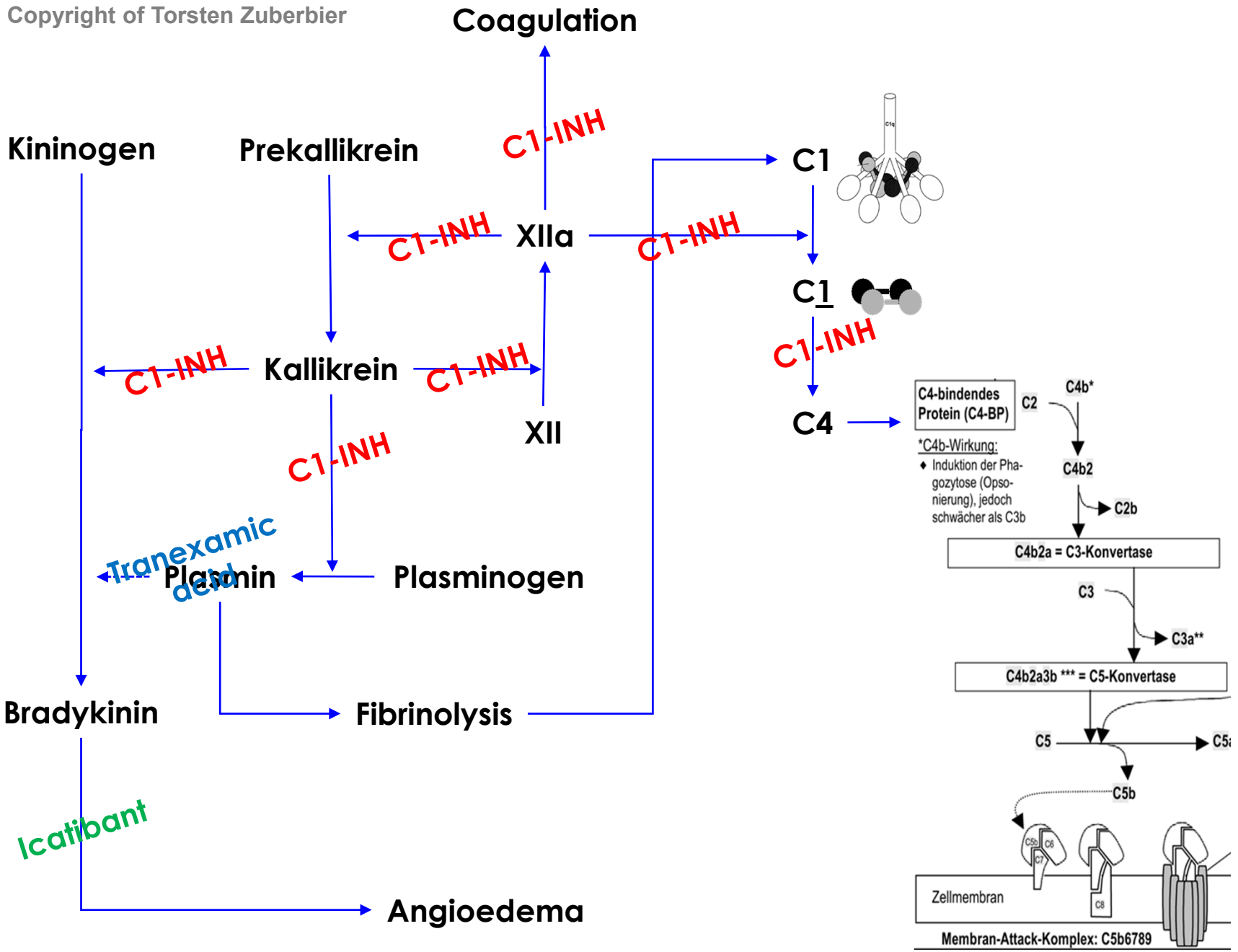

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Therapy of HAE

acute attack

short term prophylaxis

(special risk following trauma)
prophylactic treatment before surgery

long term prophylaxis

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Therapy of acute HAE attacks with C1-INH

- laryngeal or facial edema or painful abdominal spasms or disabling swelling

- blood product

- 20 U per kg body weight i.v. (75kg ≈ 3 ampullas à 500 U)

- fast relief, therapy is well tolerated

Price for Berinert®: 1 ampoule costs 891,80 €

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Therapy of acute HAE attacks with Icatibant

- laryngeal or facial edema or painful abdominal spasms or disabling swelling
- 30 mg per injection s.c.
- fast relief, therapy is well tolerated

Price for Icatibant: 1 ampoule costs 2.175,00 €

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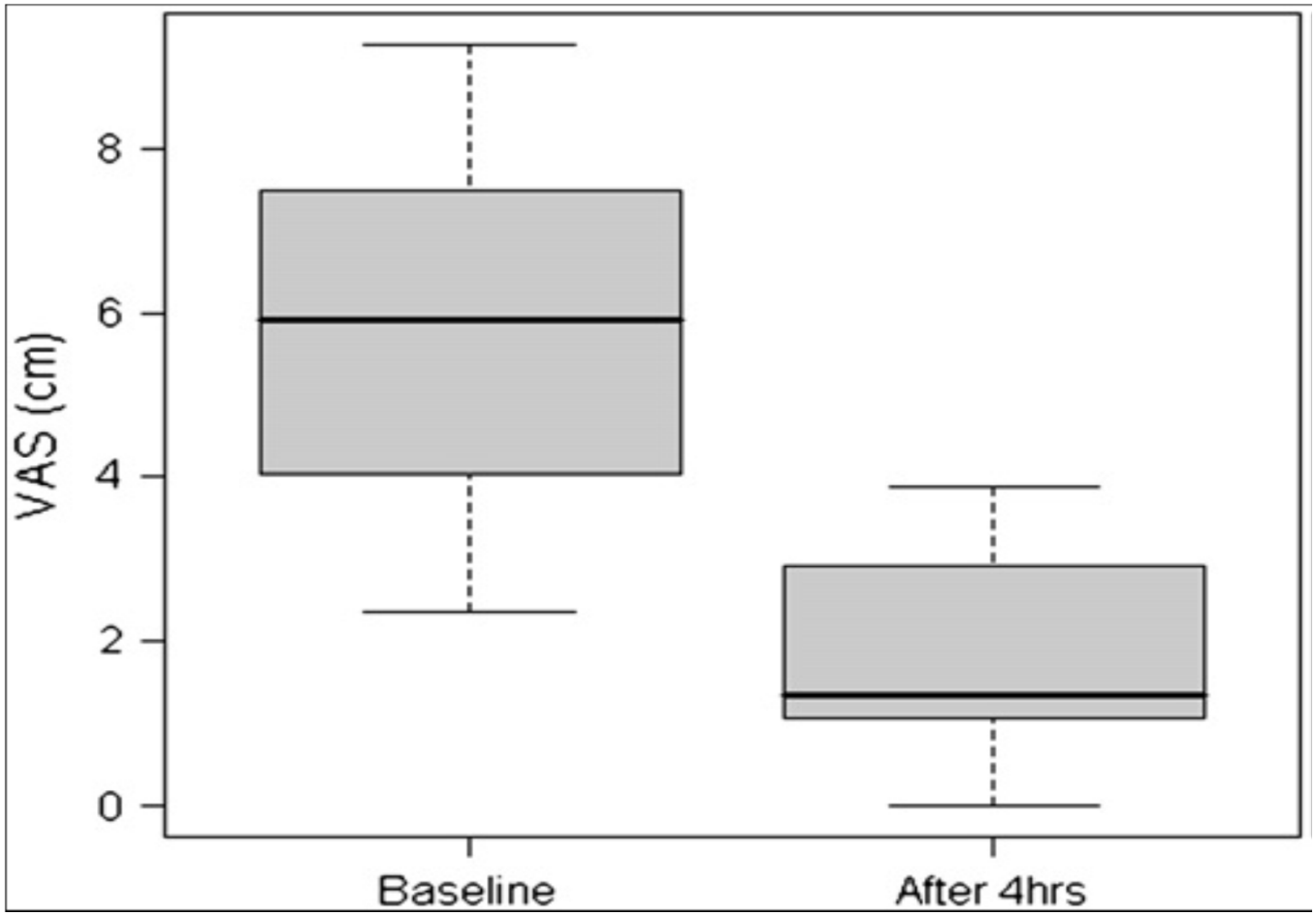
Percentage based on Symptom severity before and after 4 hours onset of treatment with Icatibant



Bork et al. J Allergy Clin Immunol, 119 (6): 1497-1503, 2007.

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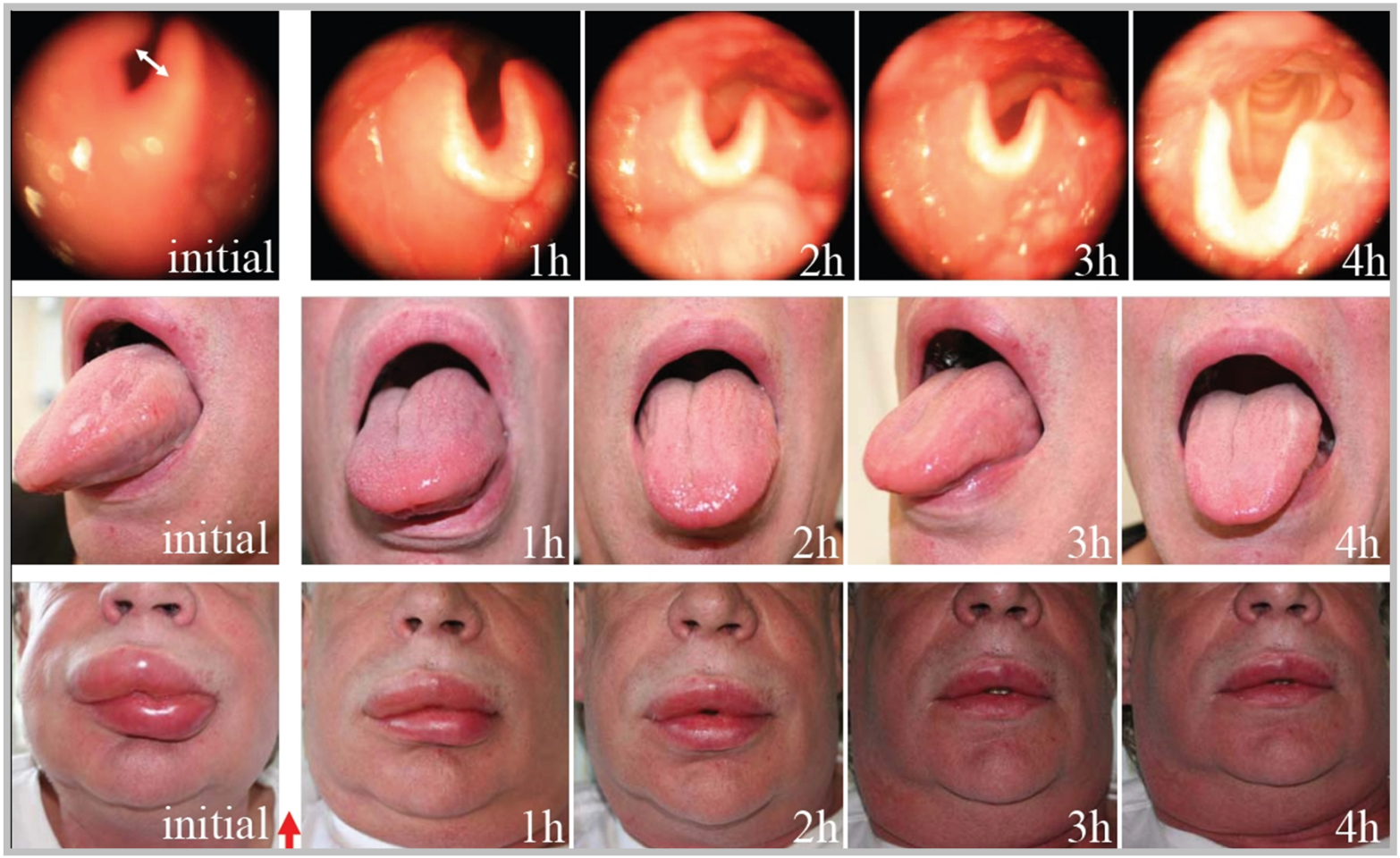
Bradykinin antagonist = angioedema treatment



Bas et al., *Allergy* 2006 andBas et al., *Allergy* 2007

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Short term prophylaxis

minor operations:

C1-INH replacement on hand

or

5 days before to 2 days after:
Danazol 10mg/kg BWdaily, max. 600mg p.diem

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Short term prophylaxis

any oro-pharyngeal operation or larger operations:

C1-INH 1 hour before:
500 <50kg BW
1000 >50kg BW
1500 >100kg BW

have a second dose on hand !

Observe for >36 hours (in patient)

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Long term prophylaxis with danazol

initially 200mg daily.

taper down if possible

then reduce to minimal effective dose (50-100mg)

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Long term prophylaxis with danazol

Danazol side effects at high dosage:

- toxic liver damage
- hemorrhagic cystitis
- hypercholesterinemia
- Polyglobulämia

Danazol side effects low dosage:

- increase of body weight
- loss of libido
- acne
- menstruation/cycle disorders, virilisation

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Long term prophylaxis with TA

Not everywhere available, e.g.in Germany

risk of thrombosis

unreliable effectivity

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Summary Therapy of HAE

acute:	prophylactic:
maintain airways free	Danazol short term
C1-INH 20U i.v. per kg BW	Danazol long term <200mg
Icatibant 30mg s.c.	Tranexamic acid

… and educate well !!

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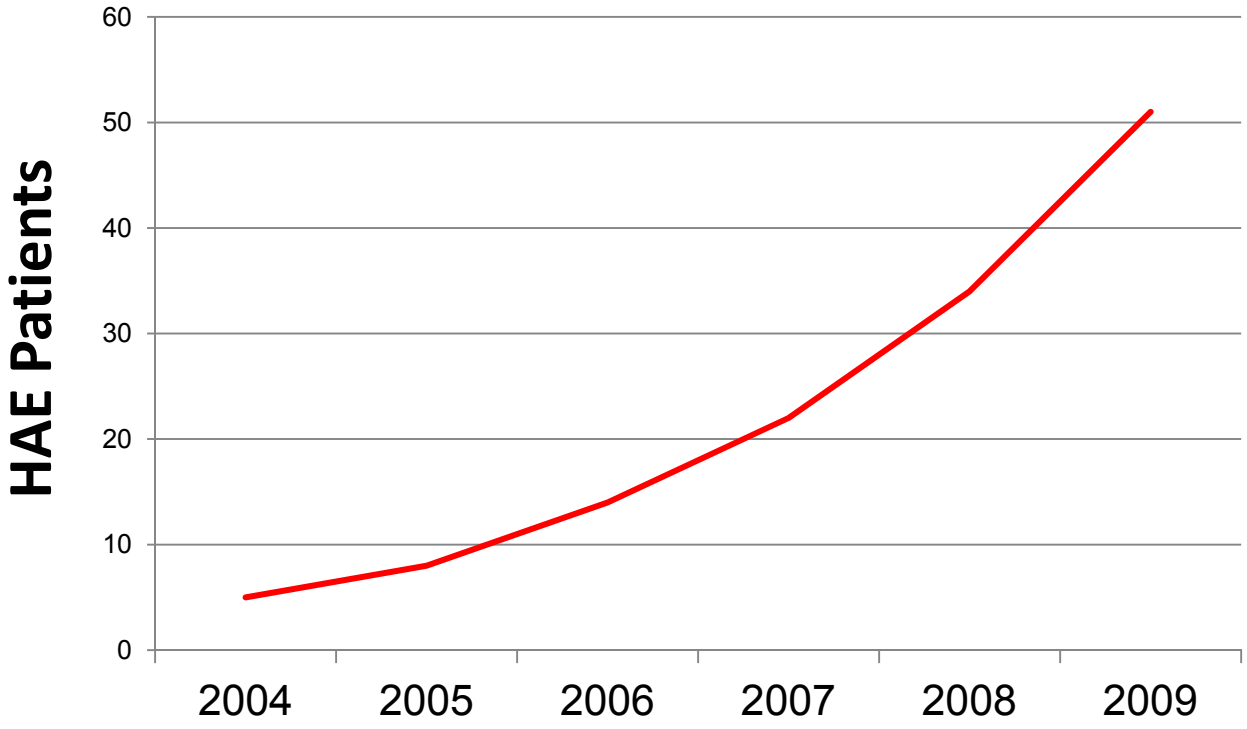
ANGIOÖDEM
SPRECHSTUNDE

74
Today



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Out- and Inpatient Clinics

- 600+ angioedema patients/year
- 74 HAE I / II
- HAE III / AAE / Pediatric population

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Angioedema Team

Dr. Markus Magerl

ANGIOÖDEM
SPRECHSTUNDE

CHARITÉ

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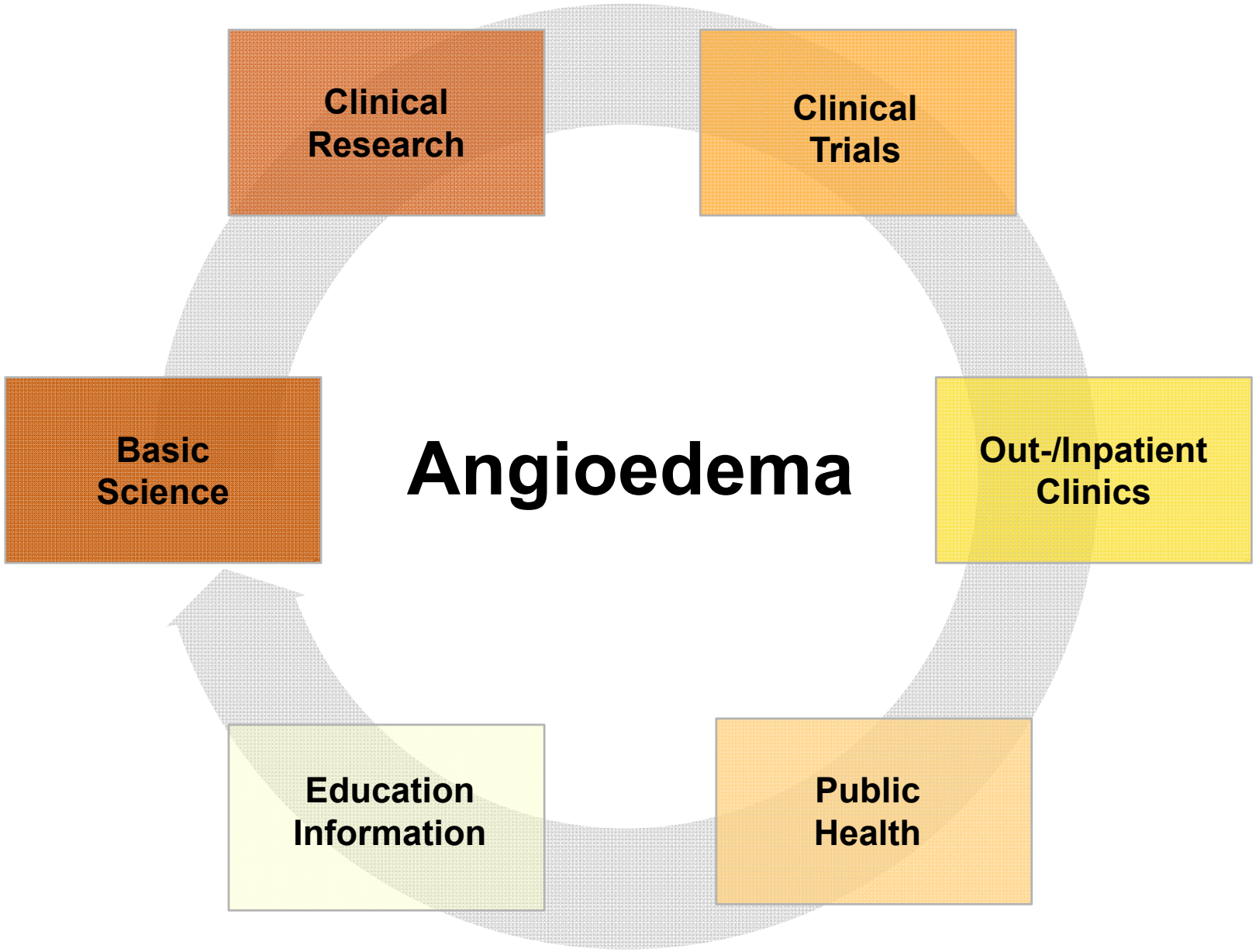

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Case report 1

- 53 year old female
- AEs since childhood (1-2/y)

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Case report 1

- 53 year old female
- AEs since childhood (1-2/y)
- Appendectomy 1968, Hysterectomy 1994
- 6/2008 diagnosed with type II HAE

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Case report 1

- 53 year old female
- AEs since childhood (1-2/y)
- Appendectomy 1968, Hysterectomy 1994
- 6/2008 diagnosed with type II HAE
- 9/2008 abdominal attack

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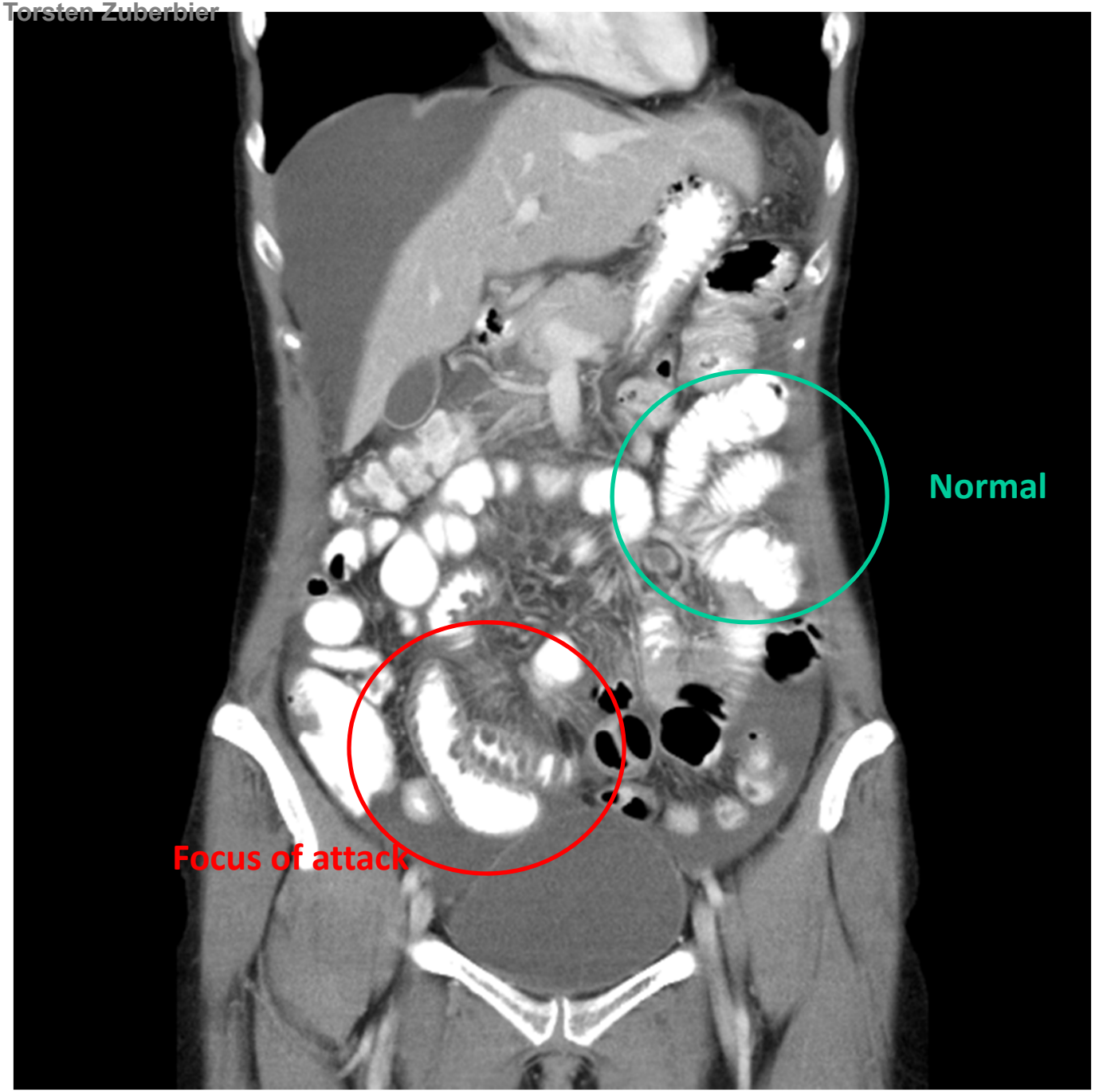

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Case report 1

- 53 year old female
- AEs since childhood (1-2/y)
- Appendectomy 1968, Hysterectomy 1994
- 6/2008 diagnosed with type II HAE
- 9/2008 abdominal attack
- Firazyr → effective after 30 min

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Case report 1

- 53 year old female
- AEs since childhood (1-2/y)
- Appendectomy 1968, Hysterectomy 1994
- 6/2008 diagnosed with type II HAE
- 9/2008 abdominal attack
- Firazyr → effective after 30 min
- 10/2008 AE lip, chin, neck
- Firazyr → complete remission after 2h

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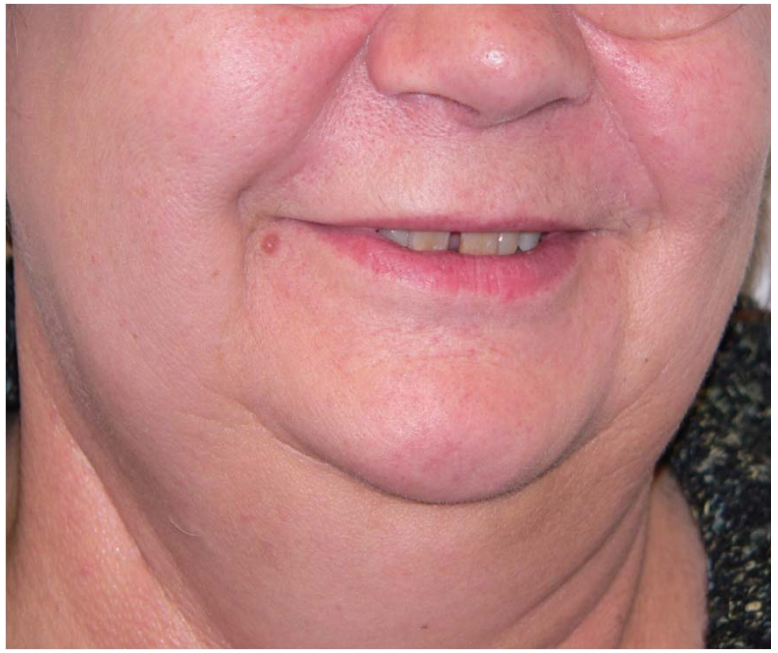
AE lip, chin, neck



3 hours after Firazyr

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First successfull treatment of AAE with Firazyr

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Case report 2

- 62 year old female
- 1/2008 diagnosed with B-Non-Hodgkin-Lymphoma

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Case report 2

- 62 year old female
- 1/2008 diagnosed with B-Non-Hodgkin-Lymphoma
- AEs as of 7/2008 (up to 2x/week)
- C1 level and function ↓↓↓, AA C1q/C1 negativ
- Diagnosed with type II AE

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Case report 2

- 62 year old female
- 1/2008 diagnosed with B-Non-Hodgkin-Lymphoma
- AEs as of 7/2008 (up to 2x/week)
- C1 level and function $\downarrow\downarrow\downarrow$, AA C1q/C1 negativ
- Diagnosed with AAE
- 11/2008: pronounced lip swelling
- Berinert 500 IE → without effect (progression)
- Firazyr → effective after 90 min (remission: 3h)

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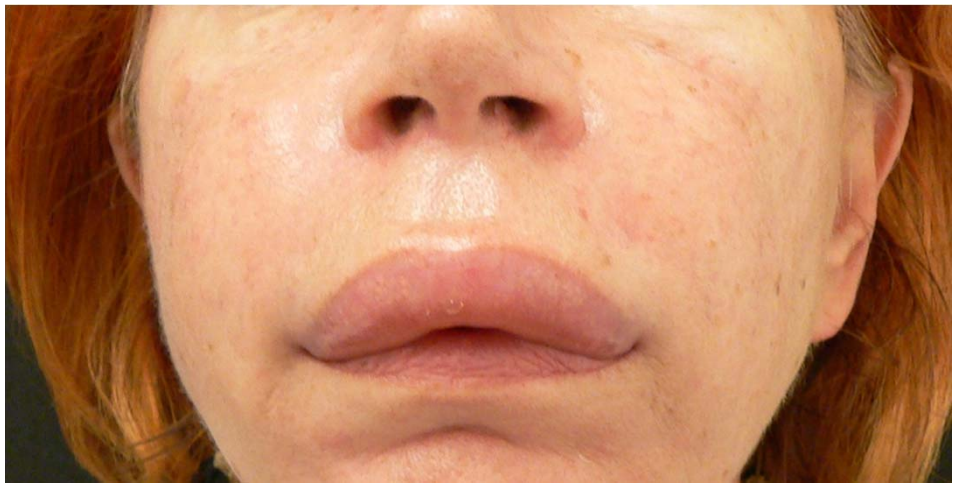

AAE upper lip, after Berinert 500 IE

3 h after Firazyr

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When to treat and when not?

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Case report 3

- 41 year old male

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Case report 3

- 41 year old male
- AEs + abdominal attacks since early childhood
- Sister died of AE when she was 9, father: mild AEs

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Case report 3

- 41 year old male
- AEs + abdominal attacks since early childhood
- Sister died of AE when she was 9, father: mild AEs
- Diagnosed with type I HAE after death of sister

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Case report 3

- 41 year old male
- AEs + abdominal attacks since early childhood
- Sister died of AE when she was 9, father: mild AEs
- Diagnosed with type I HAE after death of sister
- Past years: 4 – 6 attacks / year
- Treated with Berinert / Firazyr

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Case report 3

8/2009

acute and painful attack, right hand

To treat or not to treat?

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Case report 3

8/2009

acute and painful attack, right hand

Firazyr

Remission same night

Patient worked next day

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Thank You!