Angioedema Ereditario (HAE)

PATOGENESI, MANIFESTAZIONI CLINICHE E LINEE GUIDA DI TERAPIA IN EMERGENZA-URGENZA

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U.O. Nefrologia, Dialisi e Trapianto
Azienda Ospedaliero-Universitaria Policlinico Bari

Centro Interregionale di Riferimento per la diagnosi e cura dell'Angioedema Ereditario

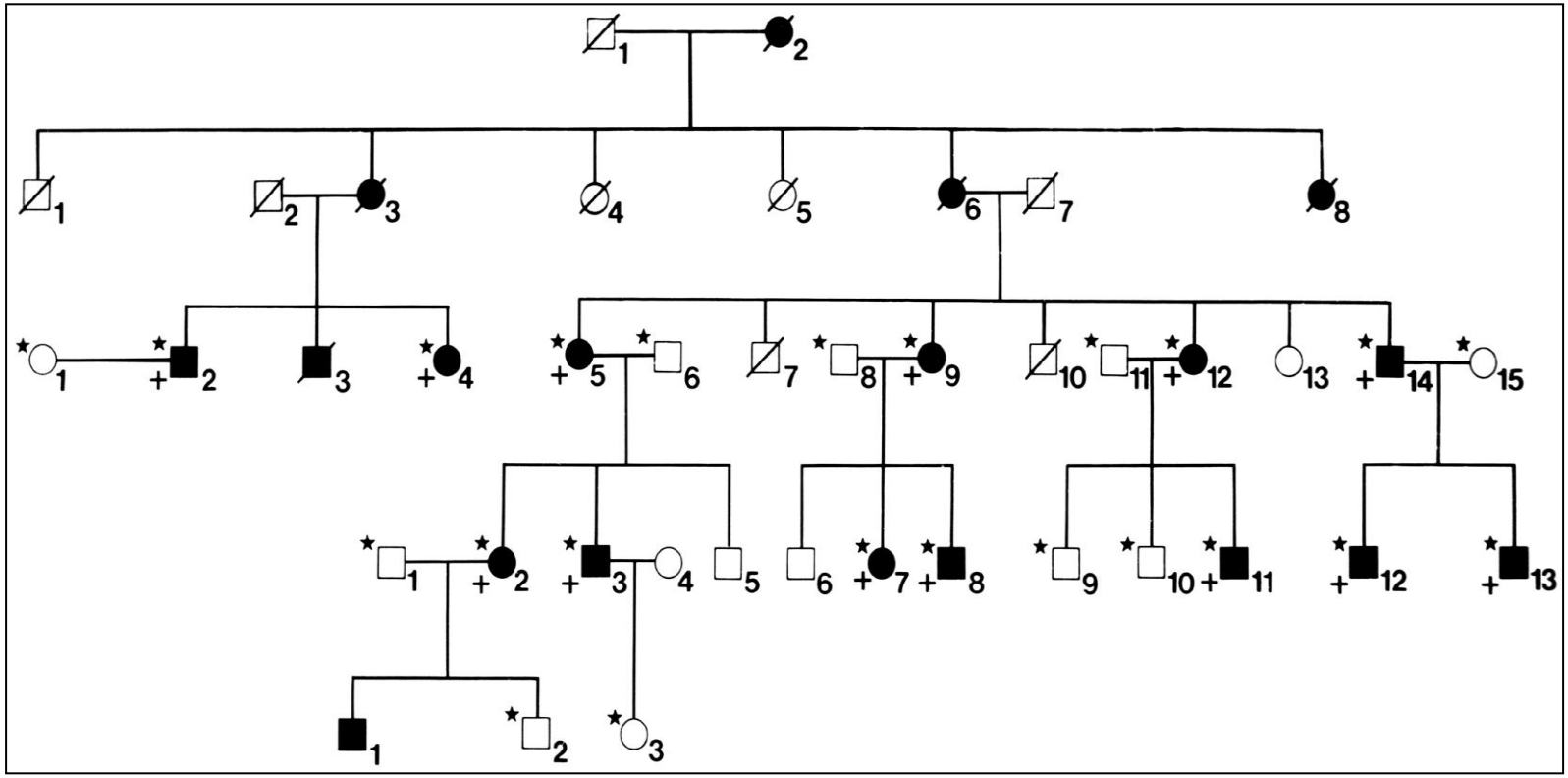
HAE - Definizione

- Malattia genetica che si trasmette con modalità autosomica dominante
- Deficit congenito di attività antigenica e/o funzionale del C1 Inibitore (C1 INH)
- Tre varianti fenotipiche:
  - Tipo I: deficit antigenico e funzionale del C1 INH (85%)
  - Tipo II: normale C1 INH antigenico, ridotta attività funzionale (15%)
  - Tipo III: livelli antigenici e funzionali di C1 INH normali, quadro clinico di angioedema ricorrente, (mutazioni F XII)

Prevalenza dell'Angioedema ereditario in Puglia

Prevalenza dell'HAE nella popolazione generale	1: 50.000
Popolazione pugliese	4.020.707
Numero stimato di pazienti in Puglia	80
"Censimento" dei pazienti pugliesi con diagnosi di HAE	57
Pazienti "in carico" al CIR Bari	41
Numero ipotetico di pazienti senza una diagnosi	23

HAE – trasmissione autosomica dominante



HAE - genetica

- Descritte quasi 300 mutazioni diverse del gene (*SERPING1* 11q 12q-13.1)
- Trasmissione mendeliana autosomica dominante
- 25% di mutazioni "*de novo*"
- Quasi sempre status di eterozigote
- Descritti tre pazienti omozigoti
- Quarto paziente con mutazione omozigote "*de novo*"

De novo homozygous mutation of the C1 inhibitor gene in a patient with hereditary angioedema

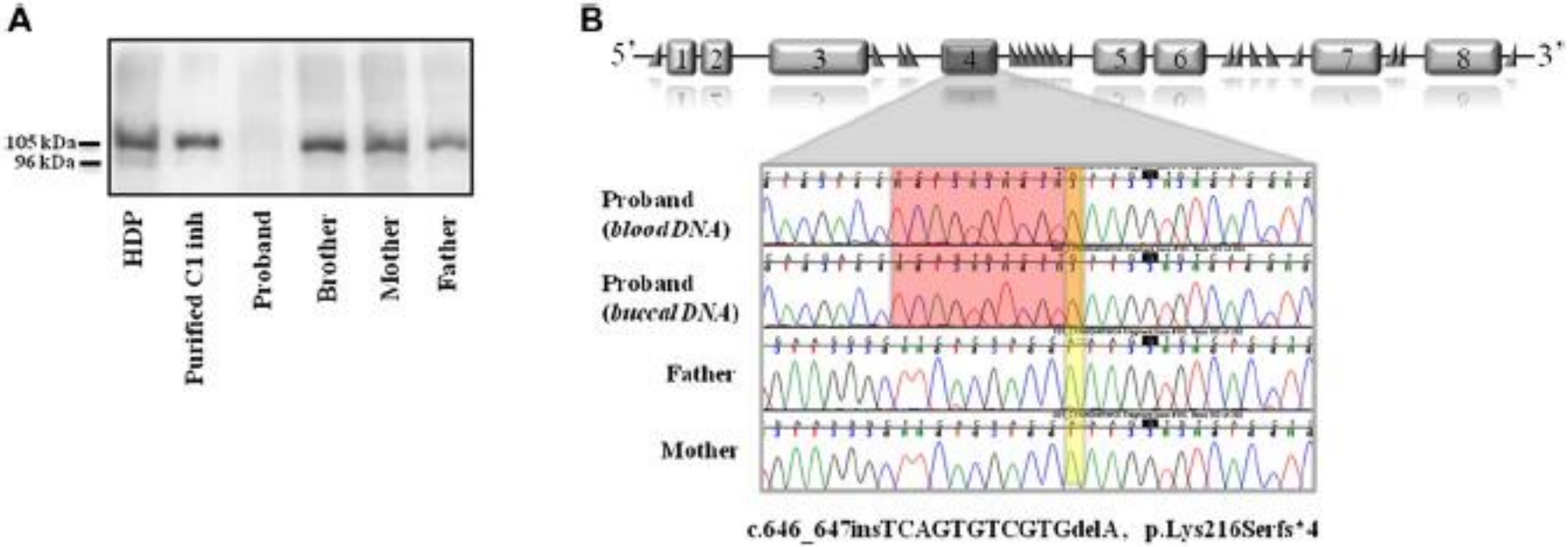
To the Editor:

Hereditary angioedema (HAE; OMIM #106100) is a rare autosomal-dominant disease resulting from congenital deficiency of C1 esterase inhibitor protein (C1-INH) that controls complement, contact-kinins, coagulation, and fibrinolytic cascades.[1] Symptoms relate to acute edema of subcutaneous tissues, viscera, and the upper airways (submucosal tissue). Edema of the larynx is

TABLE I. Clinical and laboratory features of the propositus and relatives

Parameter	Propositus	Father	Mother	Sibling
Clinical HAE	Yes	No	No	No
C1 INH antigenic (NV 21–32 mg/dL)	4	28	30	32
C1 INH functional (NV 68%-132%)	ND	108	102	104
C1q (NV 70%-130%)	83	105	93	110
C4 (NV 10-40 mg/dL)	6	18	21	19

ND, Not detectable; *NV*, normal values.



Bafunno V, et al; *J Allergy Clin Immunol* 2013; in press

HAE - diagnosi

- Angioedemi ricorrenti, non orticaria, della durata > 12 h
- Edemi laringei ricorrenti
- Familiarità positiva per attacchi di angioedema
- Attacchi ricorrenti di dolore addominale con sintomi sub-occlusivi e senza causa apparente
- Dosaggio del C1 INH (< 50% dei valori normali, antigenici e/o funzionali)
- Ridotti livelli di C4 (< 10 mg/dl)
- Tenere presente la possibilità di mutazioni "*de novo*" del gene del C1 INH (assenza di familiarità ascendente o trasversale)

Notizie Storiche

Angioedema ereditario

Die Geschichte des Quinckeschen Ödems*

Von H. Schadewaldt, Wehr, Baden

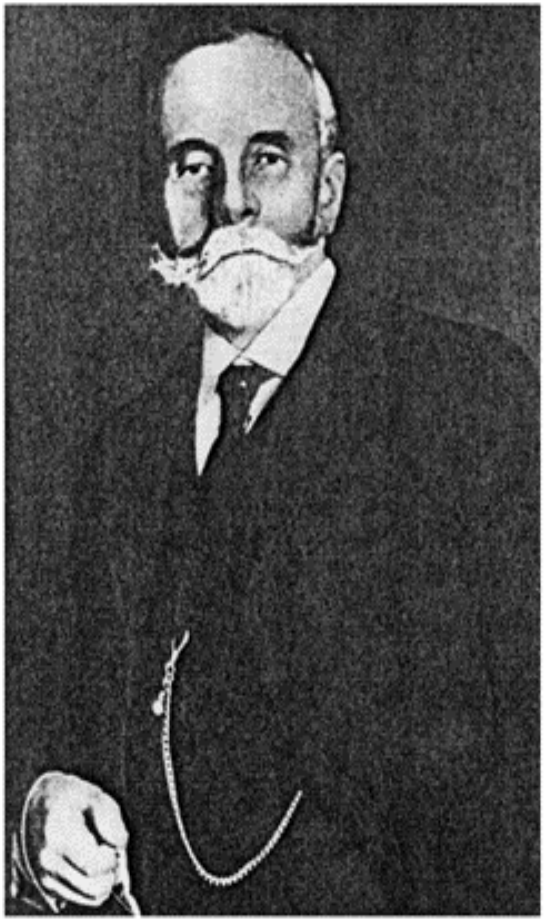


Fig. 1. Heinrich Irenaeus Quincke (1842–1922), Internist in Bern und Kiel, der 1882 das Krankheitsbild des «acuten umschriebenen Hautoedems», das heute seinen Namen trägt, umriß.

Zwölf Hefte bilden einen Band, dem Sach- u. Namen-Register u. system. Übersicht beigegeben wird.

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Dr. H. v. Hebra, Wien. Dr. O. Lassar, Berlin. Dr. P. G. Unna, Hamburg.

Band I. № 5. Juli 1882.

A. Original-Mitteilungen.

Über akutes umschriebenes Hautödem

von

H. Quincke.

Mit dem in der Überschrift genannten Namen möchte ich eine Hauterkrankung bezeichnen, die nicht so ganz selten zu sein scheint, von der aber nur wenige Fälle, mehr als Curiosa, beschrieben sind. Dr. E. Dinkelacker hat in seiner Dissertation: *Über akutes Ödem.* Kiel 1882, nach mehrern von uns beobachteten und nach den bisher beschriebenen Fällen ein Bild der Krankheit entworfen.

Dieselbe manifestiert sich in dem Auftreten ödematöser Schwellung der Haut und des Unterhautzellgewebes an umschriebenen Stellen von 2–10 und mehr Zentimeter Durchmesser. Diese Schwellungen finden sich am häufigsten an den Extremitäten, besonders in der Umgebung der Gelenke, aber auch am Rumpf und im Gesicht, hier besonders an den Lippen und den Augenlidern. Die geschwollenen Hautpartien sind nicht scharf gegen die Umgebung abgegrenzt, auch an Farbe der letztern gleich oder sogar blaß und durchscheinend, seltener etwas gerötet. Gewöhnlich empfinden die Kranken darin nur etwas Spannungsgefühl, selten Jucken. — Von ähnlichen Schwellungen können gleichzeitig auch die Schleimhäute befallen werden, so namentlich die der Lippen, des Gaumensegels, des Pharynx und Larynxeinganges, sogar bis zu solchem Grade, daß erhebliche Atemnot entsteht. Auch auf Magen- und Darmschleimhaut dürften, nach den in einem Falle anfallsweise auftretenden gastrischen und intestinalen Symptomen zu schließen, solche umschriebenen Schwellungen vorkommen. — In einem Falle traten auch wiederholte seröse Ergüsse in den Gelenken auf.

Diese Schwellungen treten nun plötzlich, gewöhnlich an mehrern Stellen zugleich auf, erreichen in einer bis einigen Stunden ihr Maximum, um eben so schnell zu verschwinden, nachdem sie mehrere

AMERICAN JOURNAL

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MEDICAL SCIENCES.

EDITED BY

I. MINIS HAYS, A.M., M.D.

NEW SERIES.

VOL. XCV.

PHILADELPHIA:
LEA BROTHERS & CO.
1888.

HEREDITARY ANGIO-NEUROTIC ŒDEMA.[1]

By William Osler, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA, PHYSICIAN TO THE UNIVERSITY HOSPITAL, TO THE PHILADELPHIA HOSPITAL, AND TO THE INFIRMARY FOR NERVOUS DISEASES.

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 236, No. 6, June 1961
Printed in U.S.A.

Partial Purification of a Serum Inhibitor of C'1-Esterase*

JACK PENSKY, LAWRENCE R. LEVY† AND IRWIN H. LEPOW‡

From The Institute of Pathology, Western Reserve University, Cleveland 6, Ohio

(Received for publication, August 22, 1960)

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.

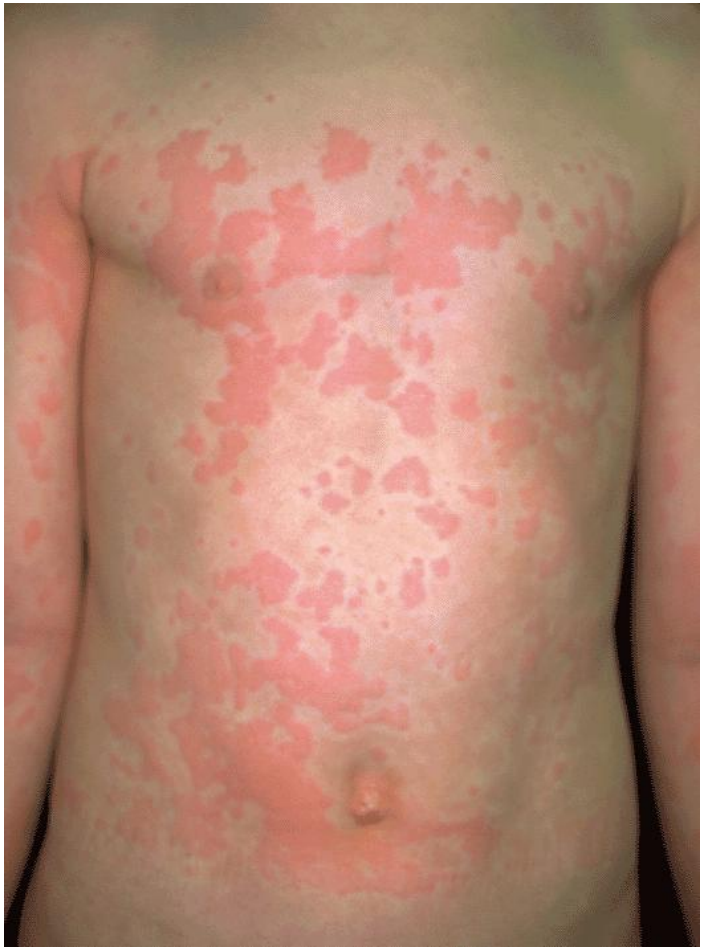
Cleveland, Ohio

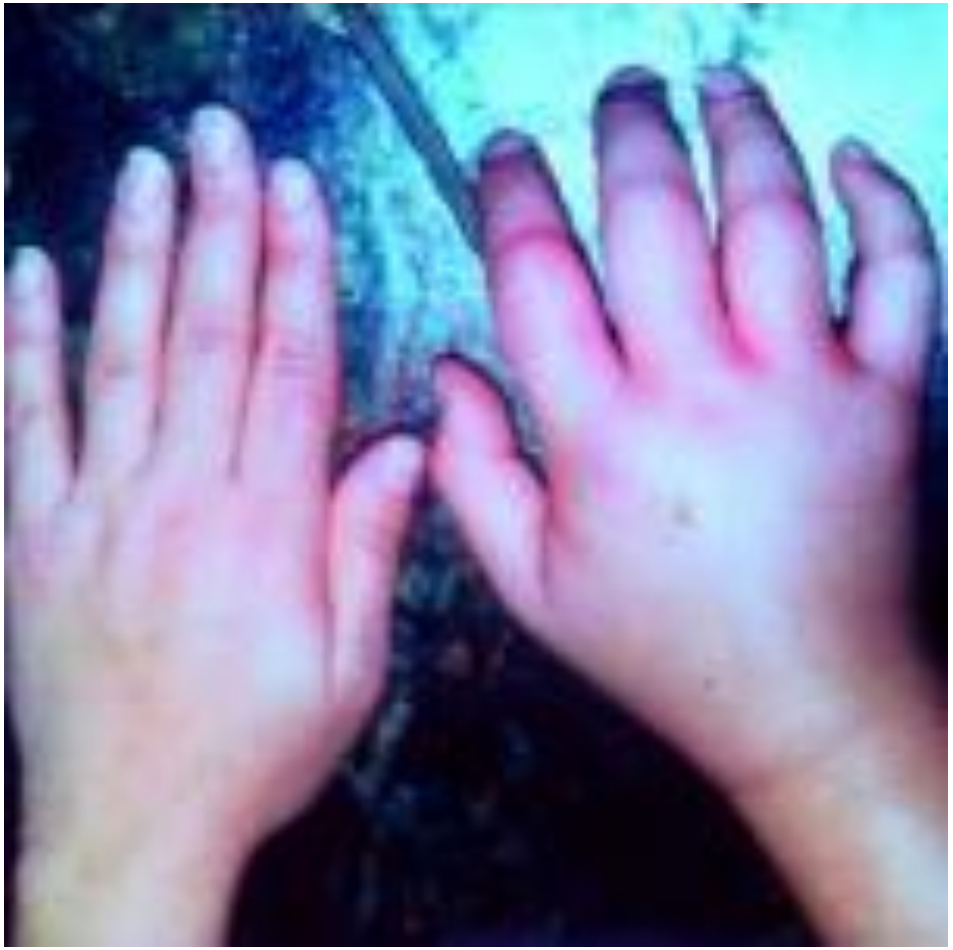
Am J Med, July 1963

Inquadramento nosologico Classificazione

Angioedema ereditario

Orticaria e Angioedema





Angioedema senza orticaria

- Angioedema allergico/istaminergico
- Deficit di C1 inibitore:
  - Congenito (HAE)
  - Acquisito (AAE)
- Angioedema indotto da farmaci
  - ACE inibitori
  - FANS
  - Estrogeni
- Angioedema associato a malattie autoimmuni
- Angioedema associato ad infezioni
- Angioedema idiopatico

Ricoveri per malattie allergiche non-asmatiche nello stato di New York

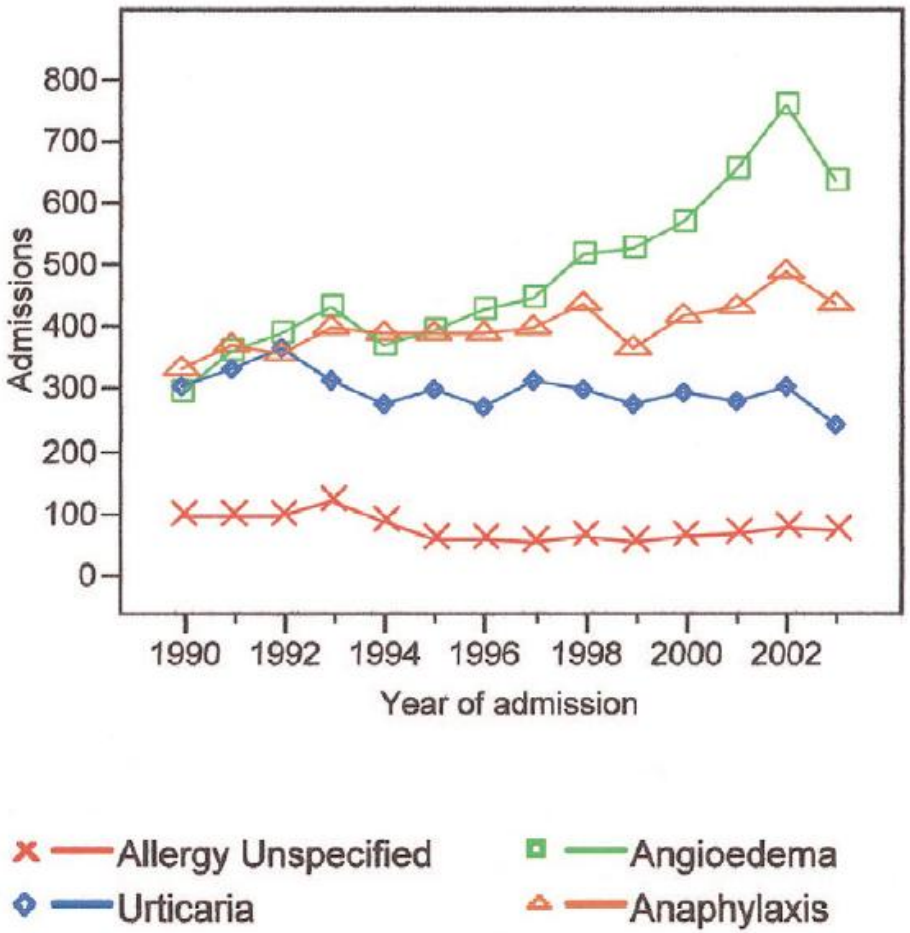
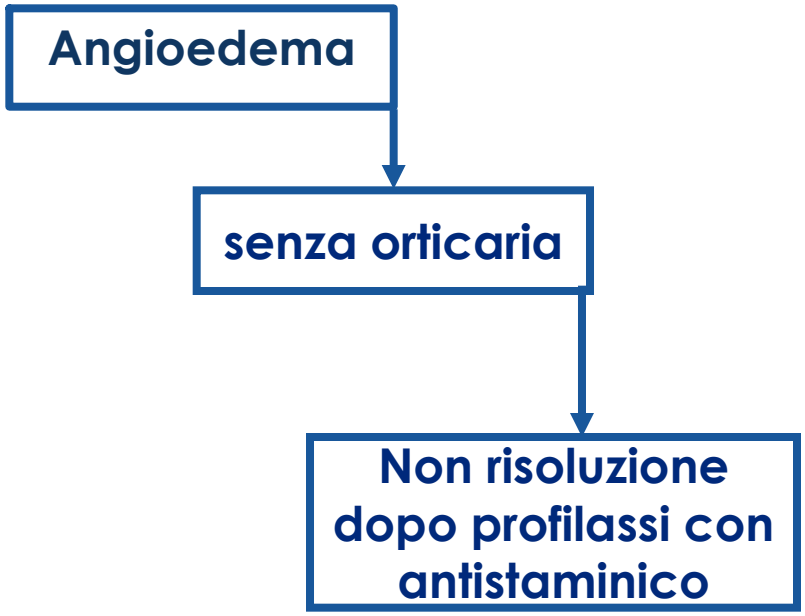


Figure 1. Hospital admissions for acute nonasthmatic diseases.

Lin RY et al; *Ann Allergy Asthma Immunol* 2005; 95:159-66

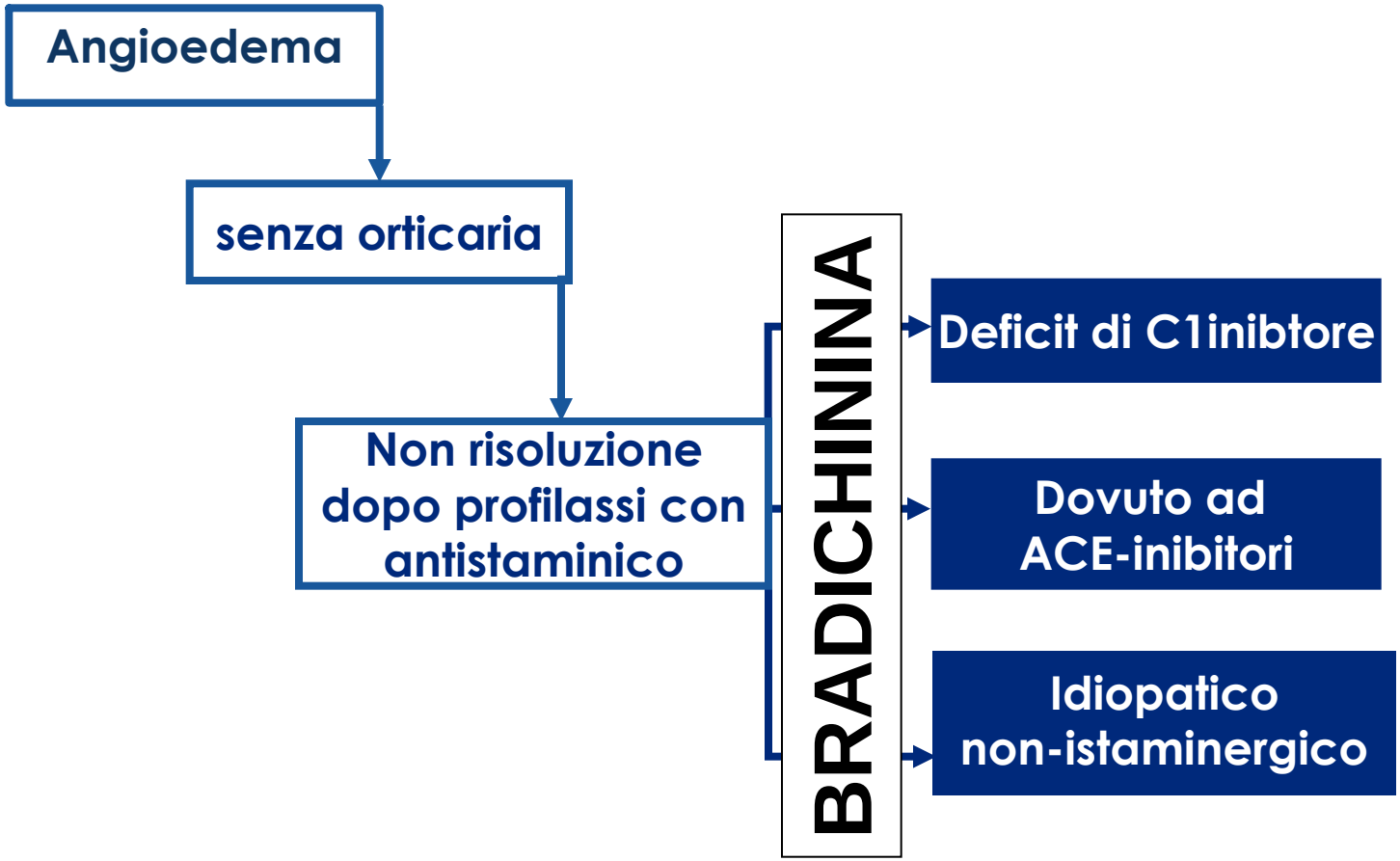
Angioedema senza orticaria

Angioedema senza orticaria



Una dose di antistaminico doppia di quella usata per riniti allergiche non previene le recidive di angioedema

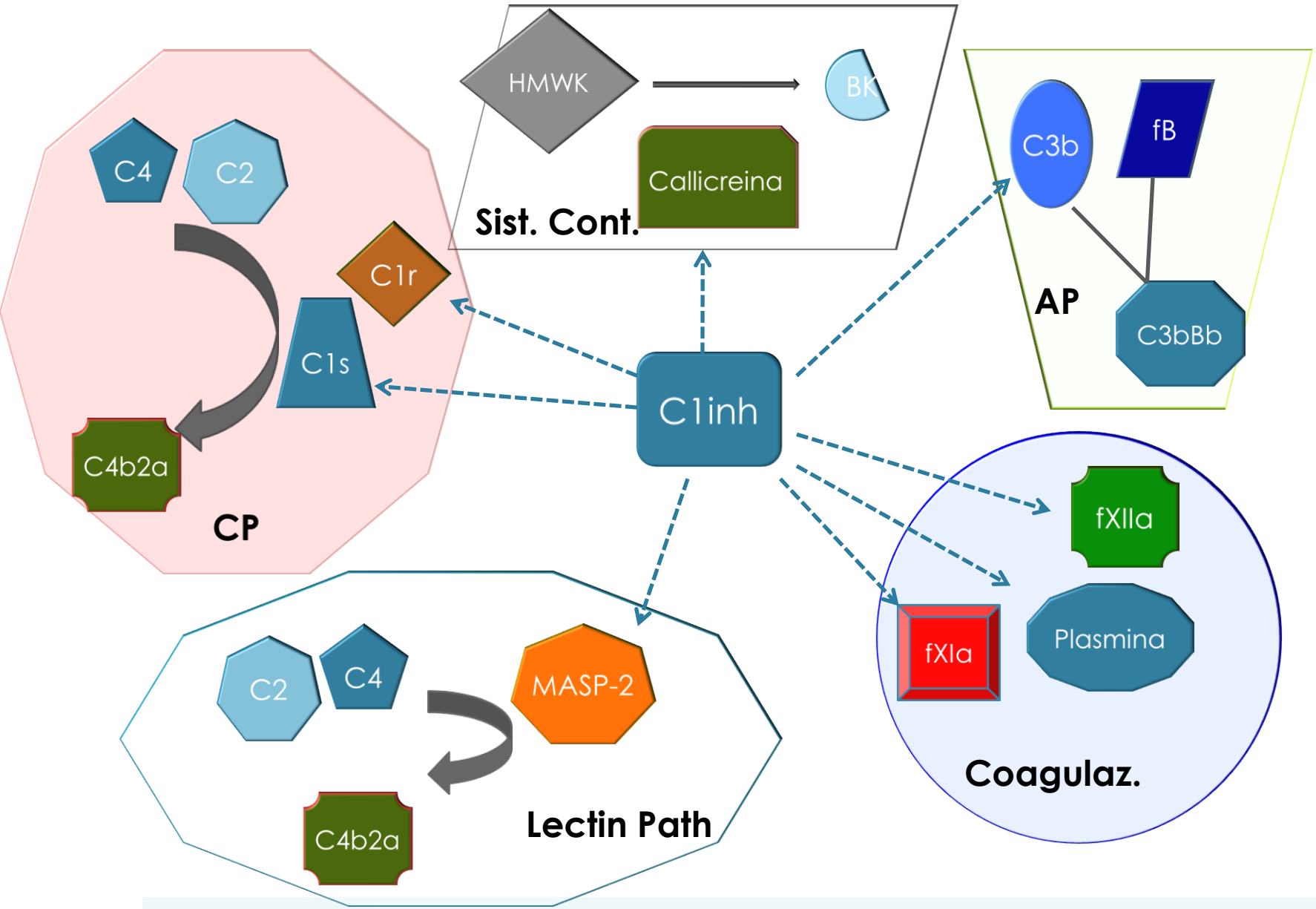
Angioedema senza orticaria



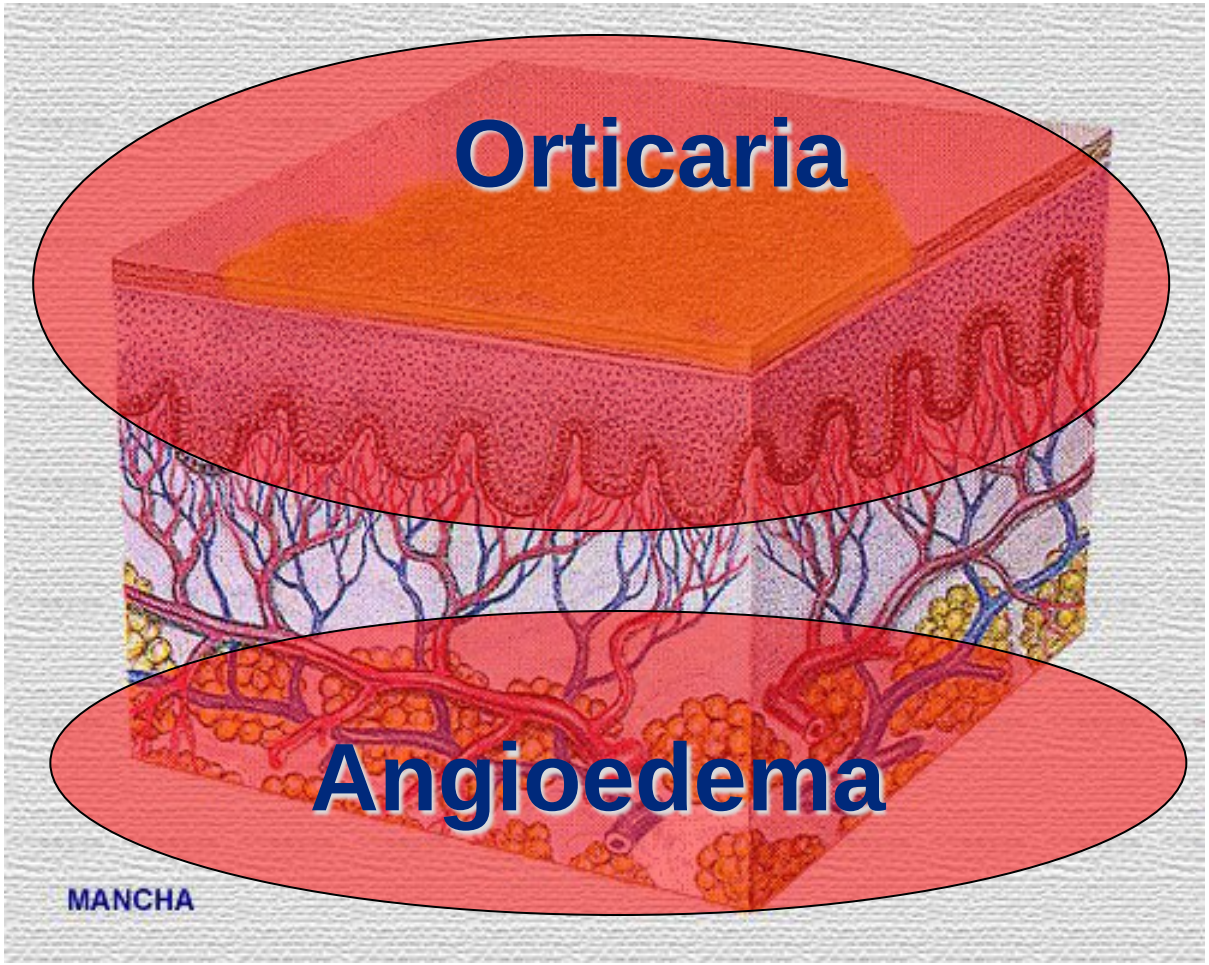
Patogenesi

Angioedema ereditario

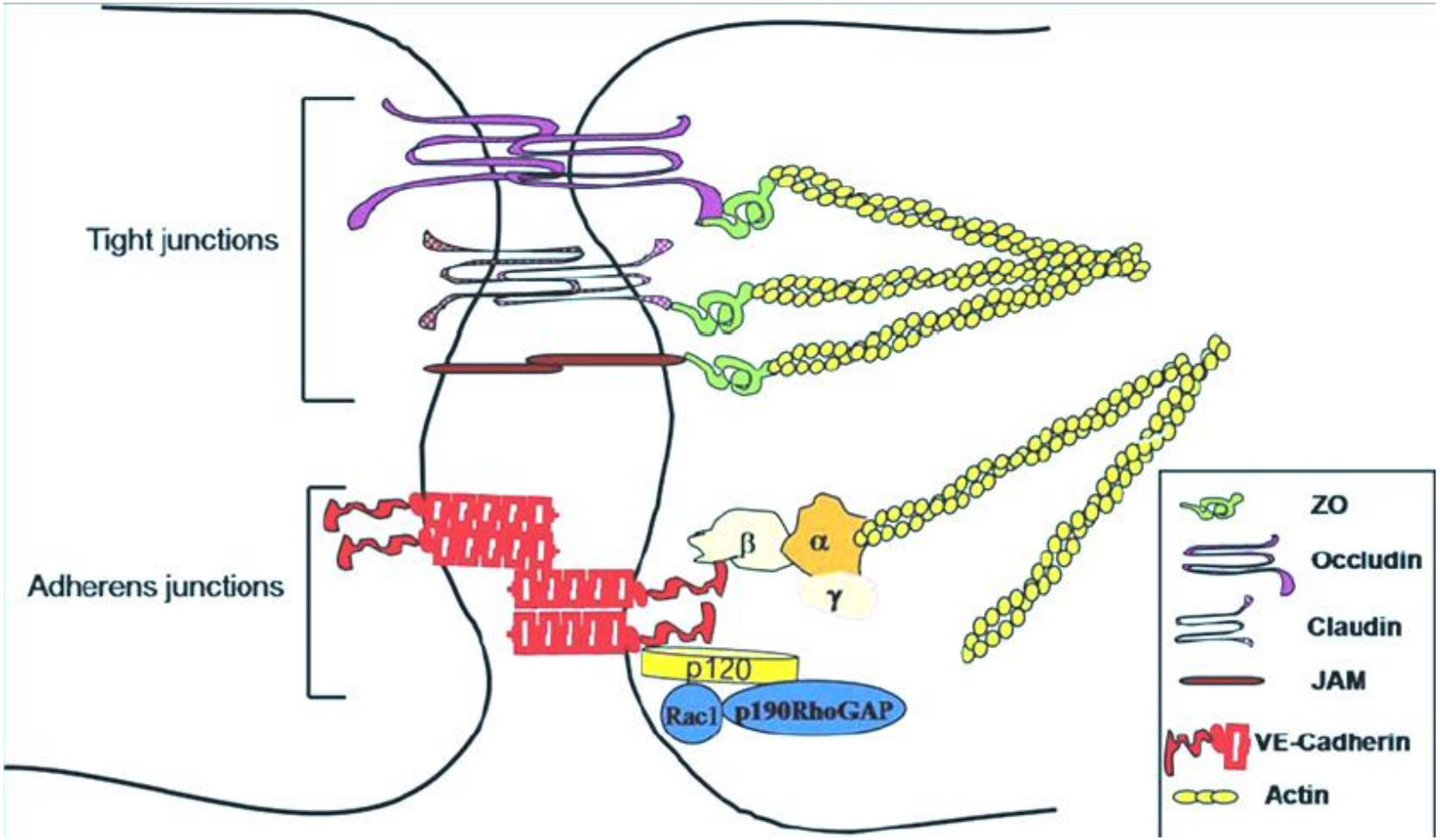
Azioni molteplici del C1 INH



Struttura della cute

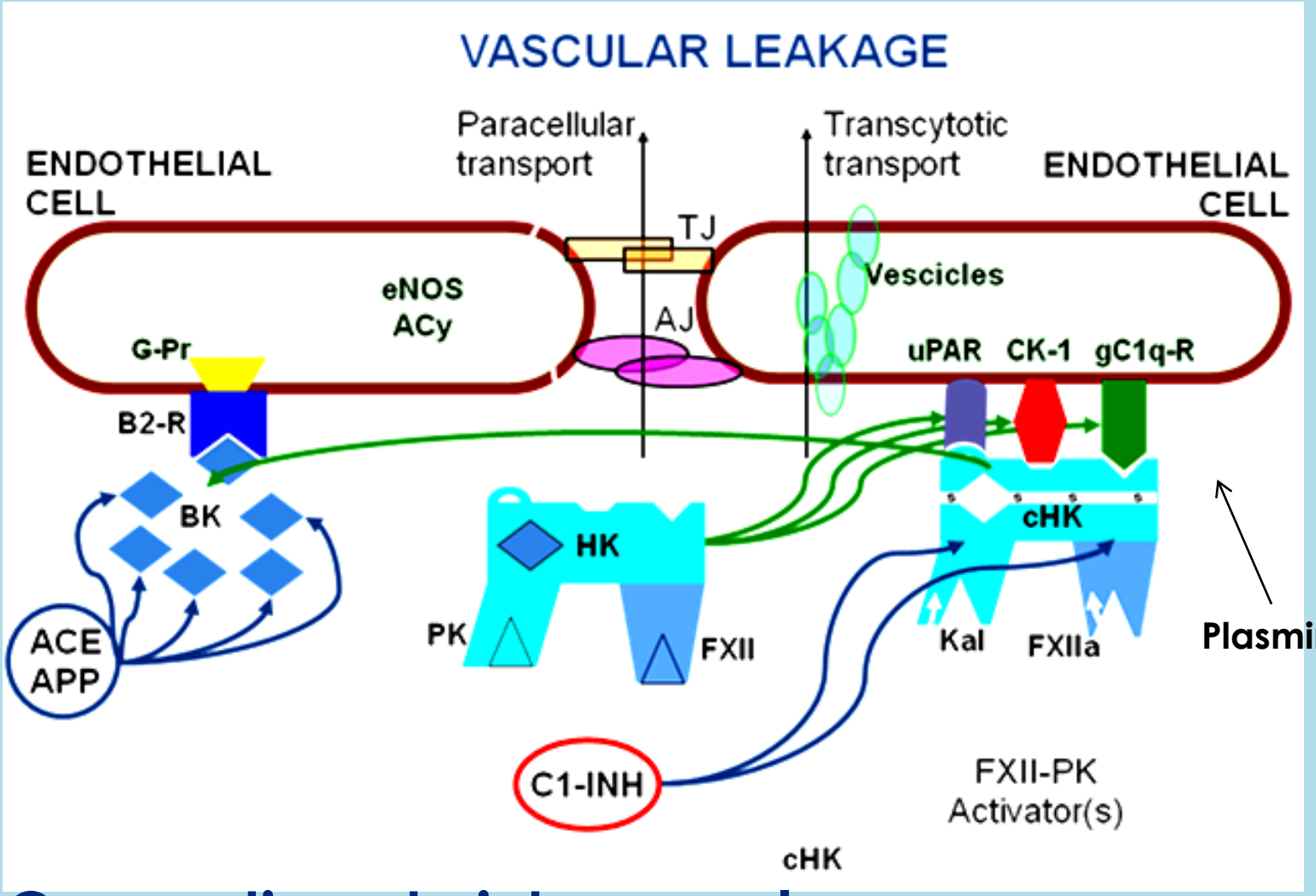


Giunzioni inter-endoteliali



Vandenbroucke et al. Ann NY Acad Sci 2008; 1123: 134–145

Compartimento extravascolare



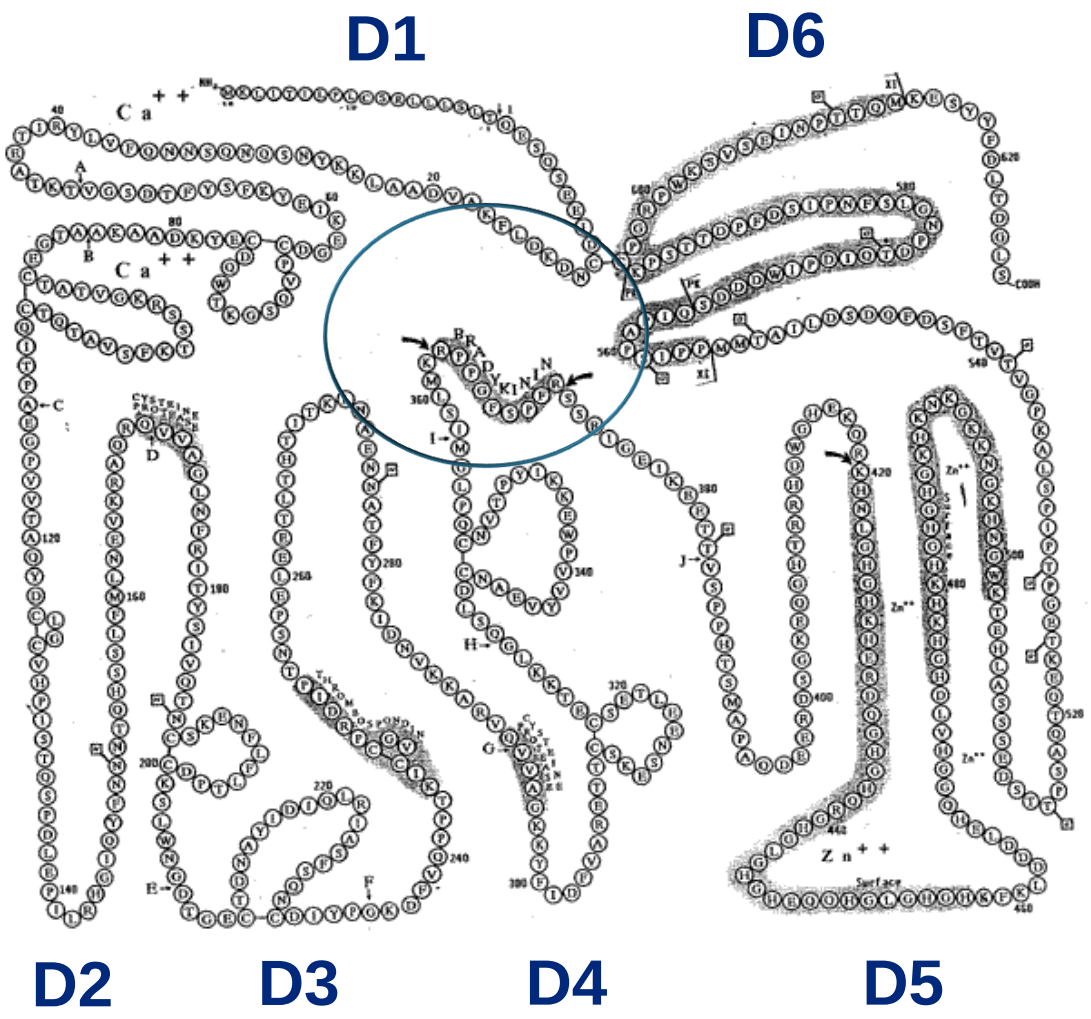
Compartimento intravascolare

Bradichinina

Bradichinina

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

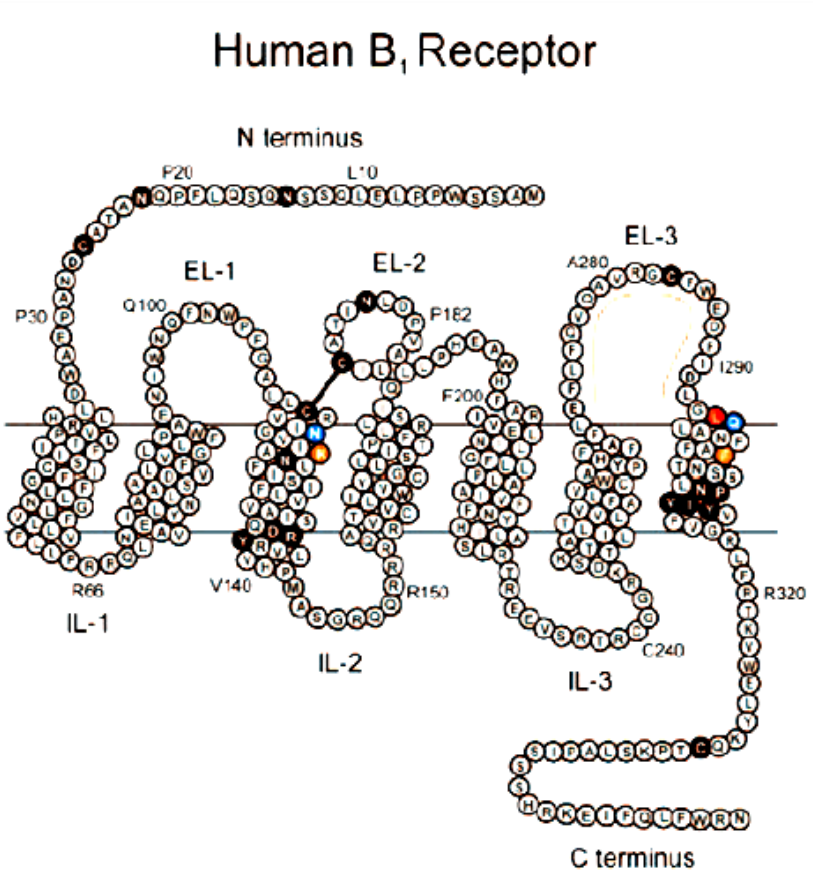
Chininogeno ad alto peso molecolare

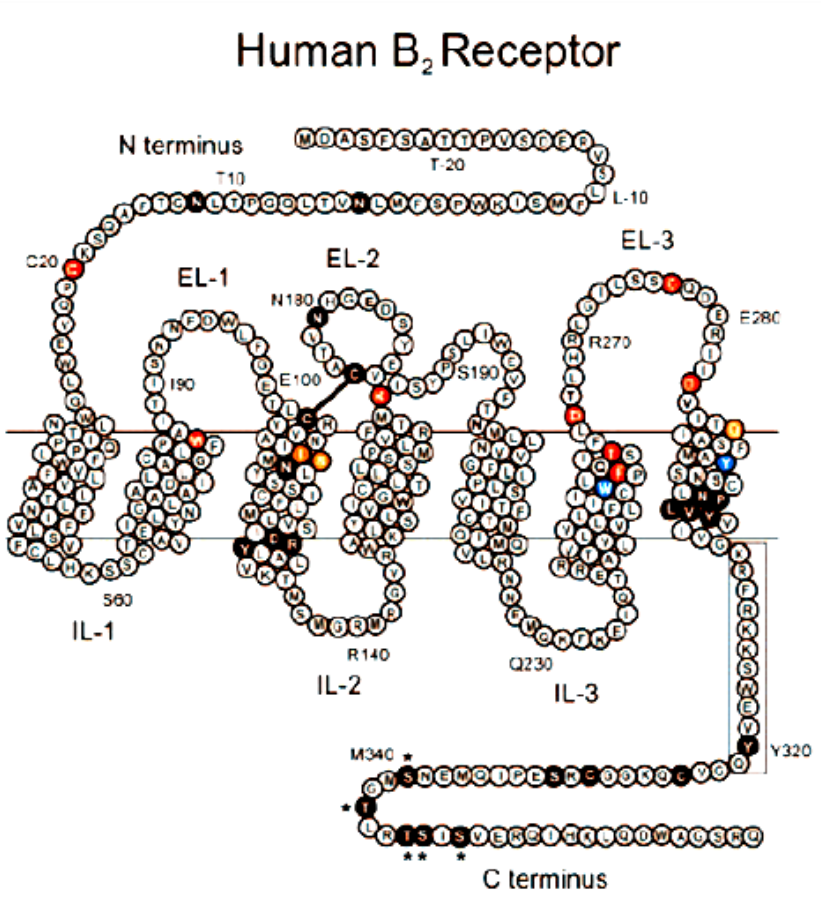


Recettori della Bradichinina

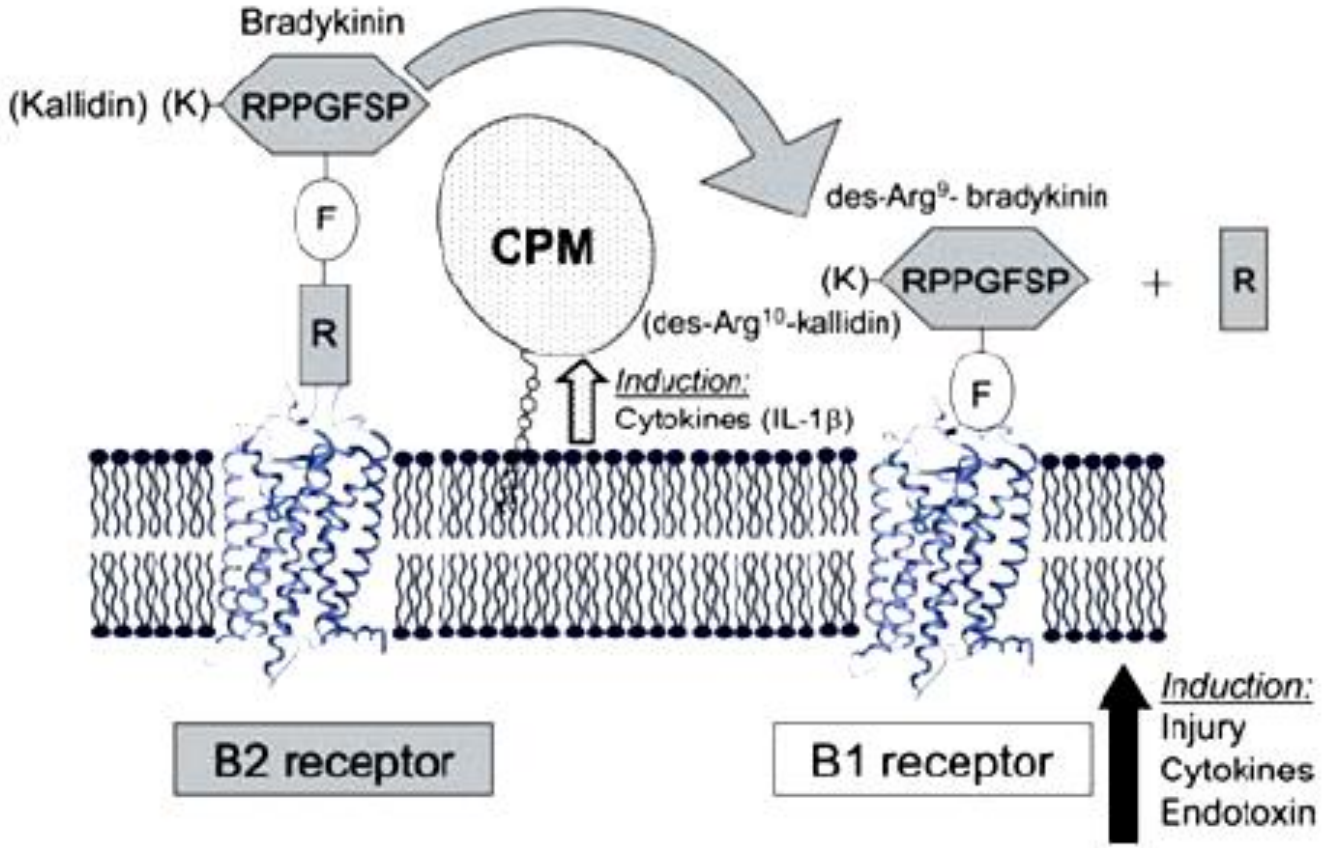
- **Recettori B1:** non espressi normalmente sulle cellule endoteliali; inducibili da stimoli pro-infiammatori (LPS, IL-1, TNF-α)
- **Recettori B2:** espressi costitutivamente sulle cellule endoteliali e muscolari lisce.
  - Vasodilatazione
  - Aumentata permeabilità vascolare
  - Broncocostrizione

Recettori BK – struttura molecolare



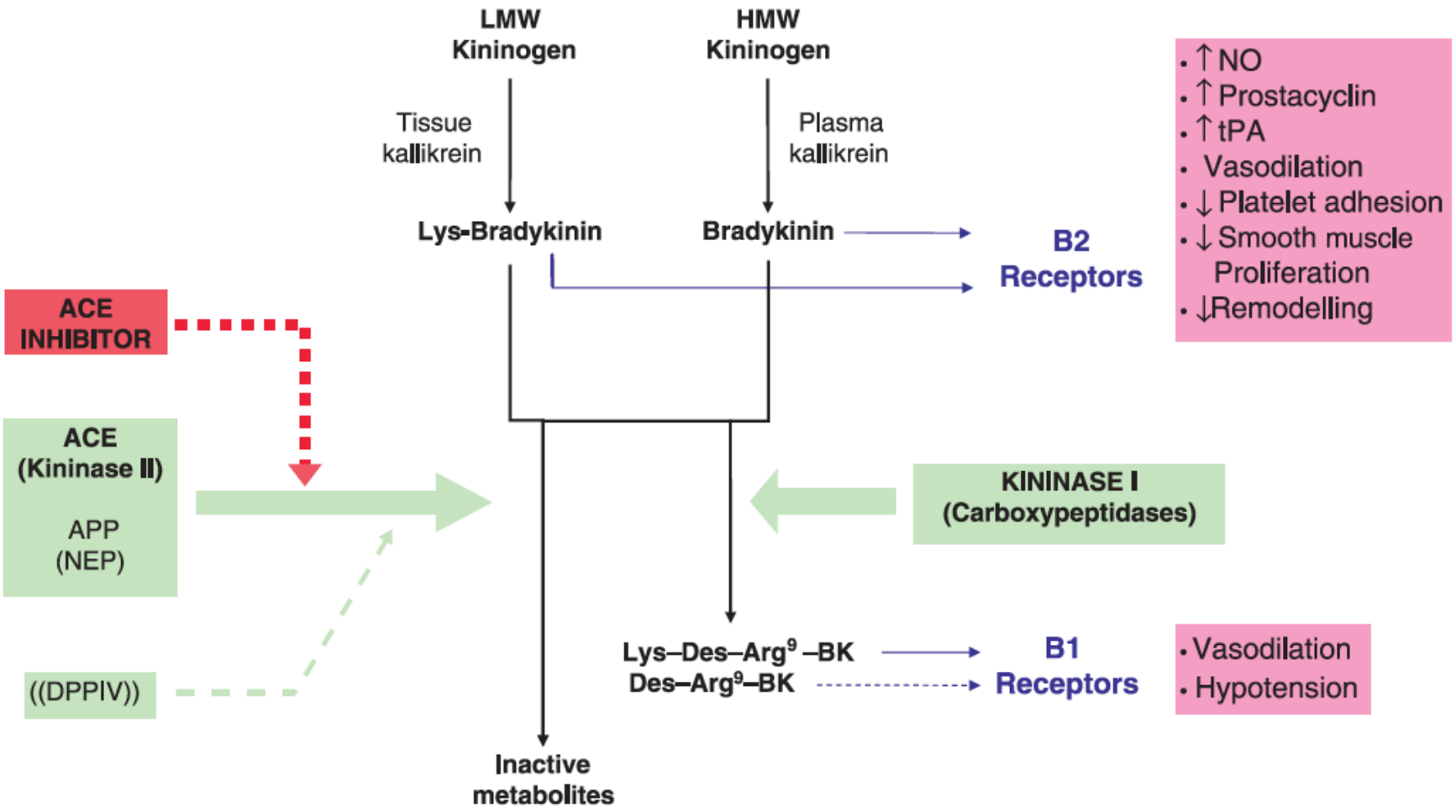


Recettori della Bradichinina



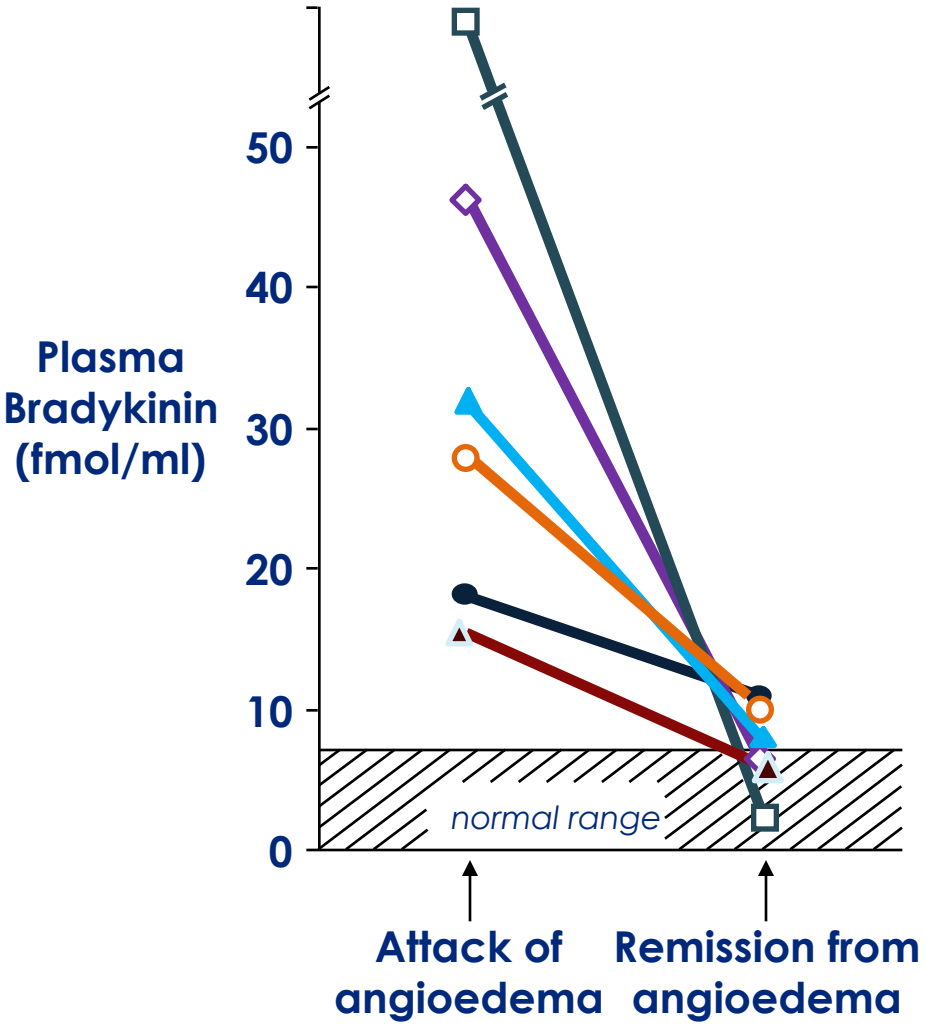
Skidgel et al. *Biol Chem 2006; 387:159–165*

BK - metabolismo



Hoover T et al, *Clin Exp Allergy* 2009; 40: 50-61

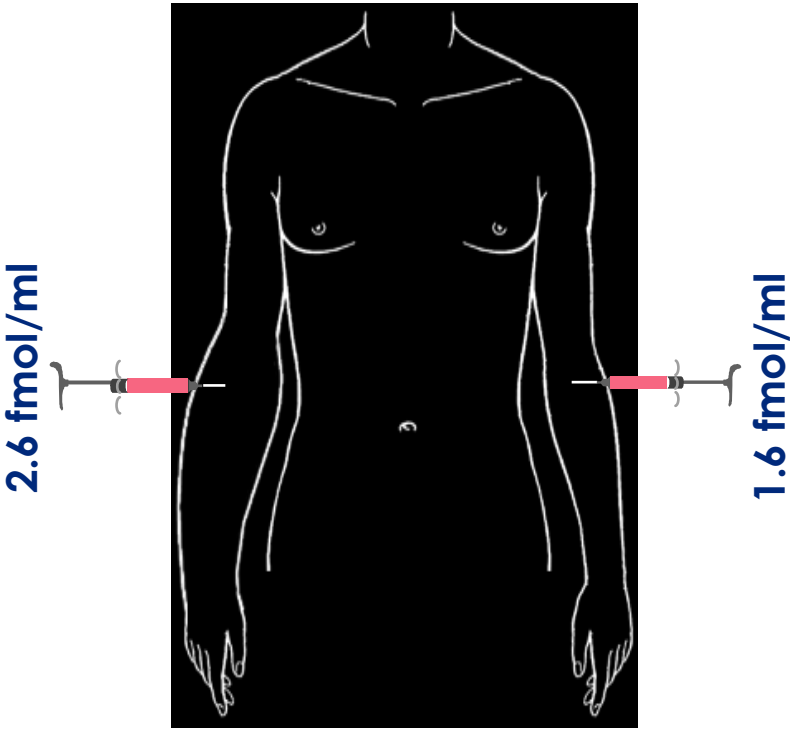
Livelli plasmatici di BK durante un attacco di AE e in fase di remissione



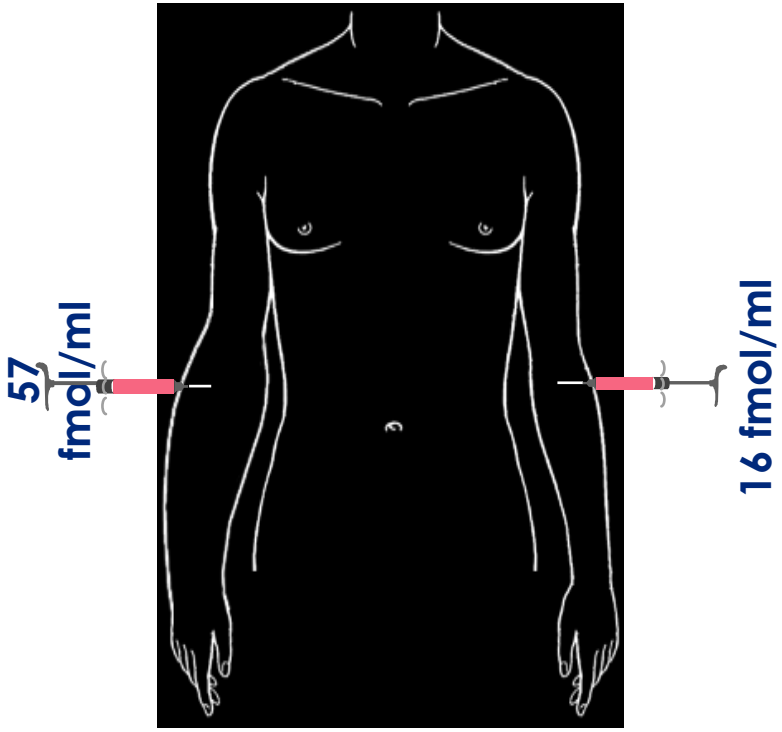
Nussberger et al, *Lancet 1998; 351: 1693-1697*

I livelli plasmatici di bradichinina aumentano in alcune forme di angioedema

Istamina-dipendente

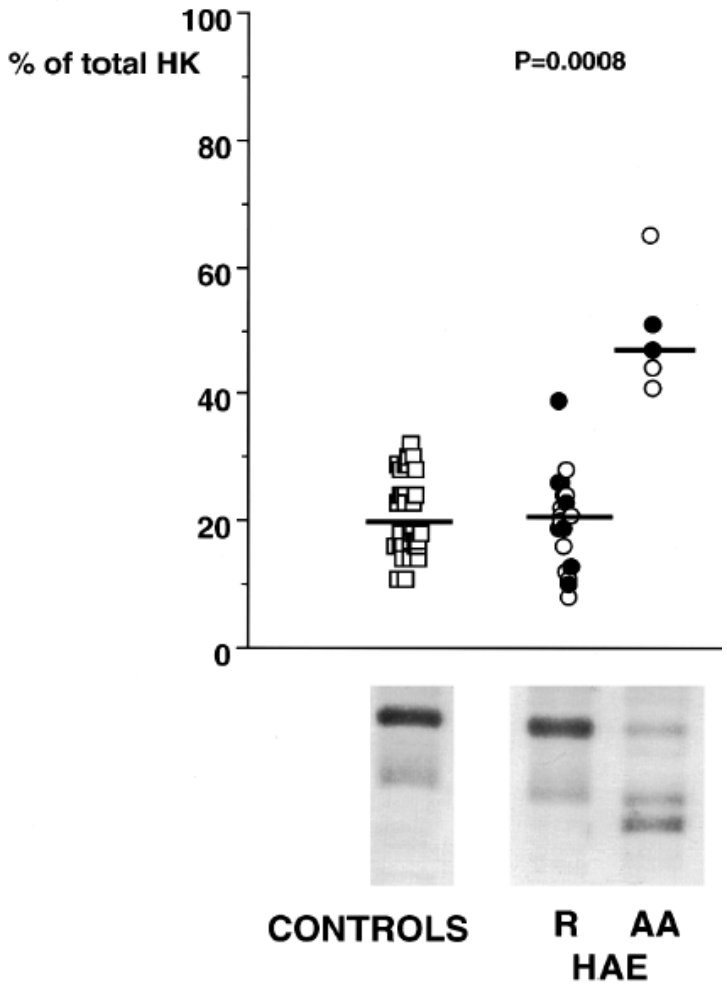


Non-istamina-dipendente



Range normale 0.2-7.1 fmol/ml

Chininogeno ad alto peso molecolare clivato negli attacchi di AE



Cugno et al; *Blood* 1997; 89: 3213-18

Manifestazioni cliniche

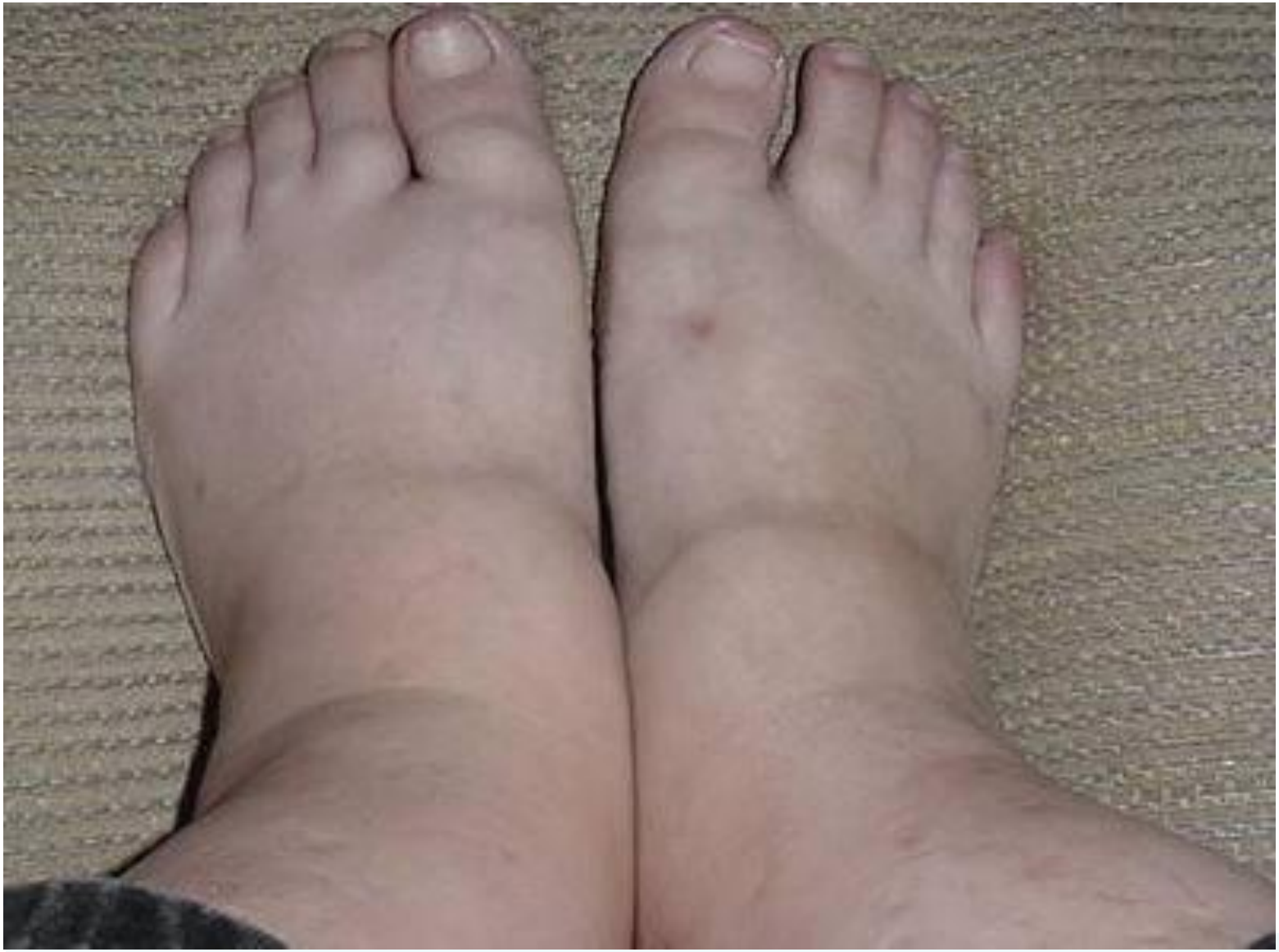
Angioedema ereditario

Quadro clinico

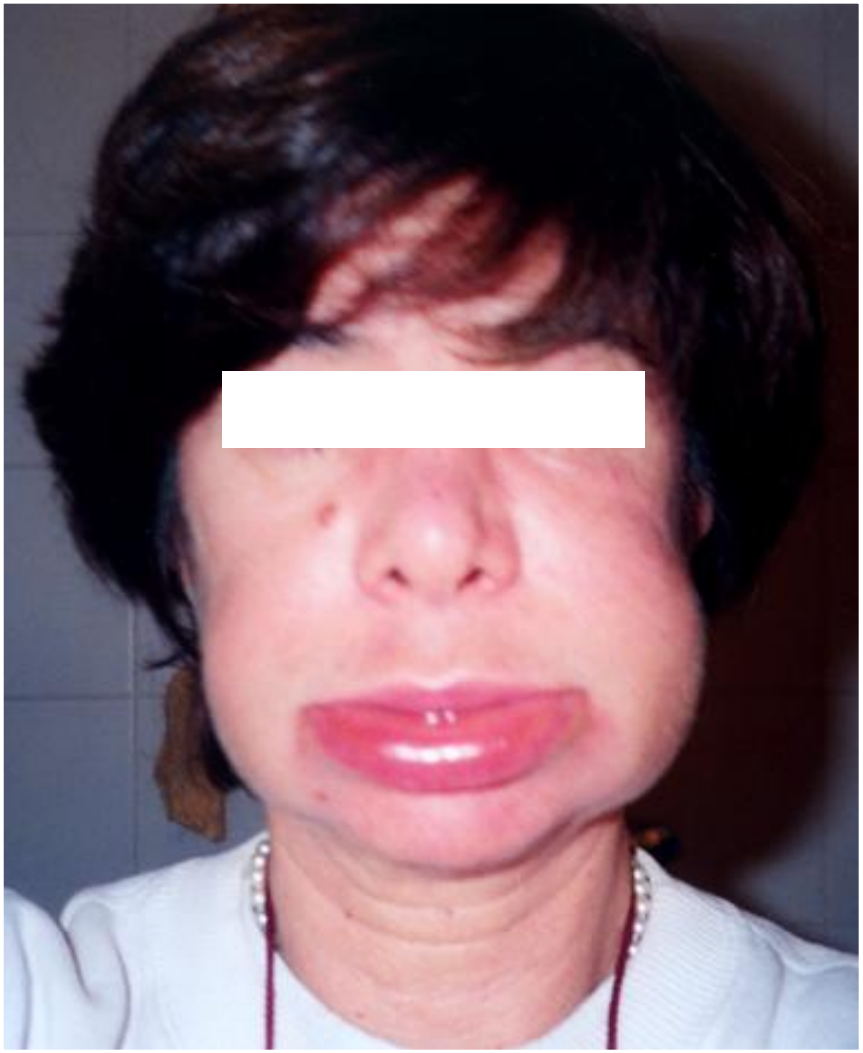
- Le manifestazioni cliniche sono caratterizzate da **angioedemi** recidivanti non flogistici e non pruriginosi, autolimitantesi, durano mediamente 3-4 giorni, che possono interessare:

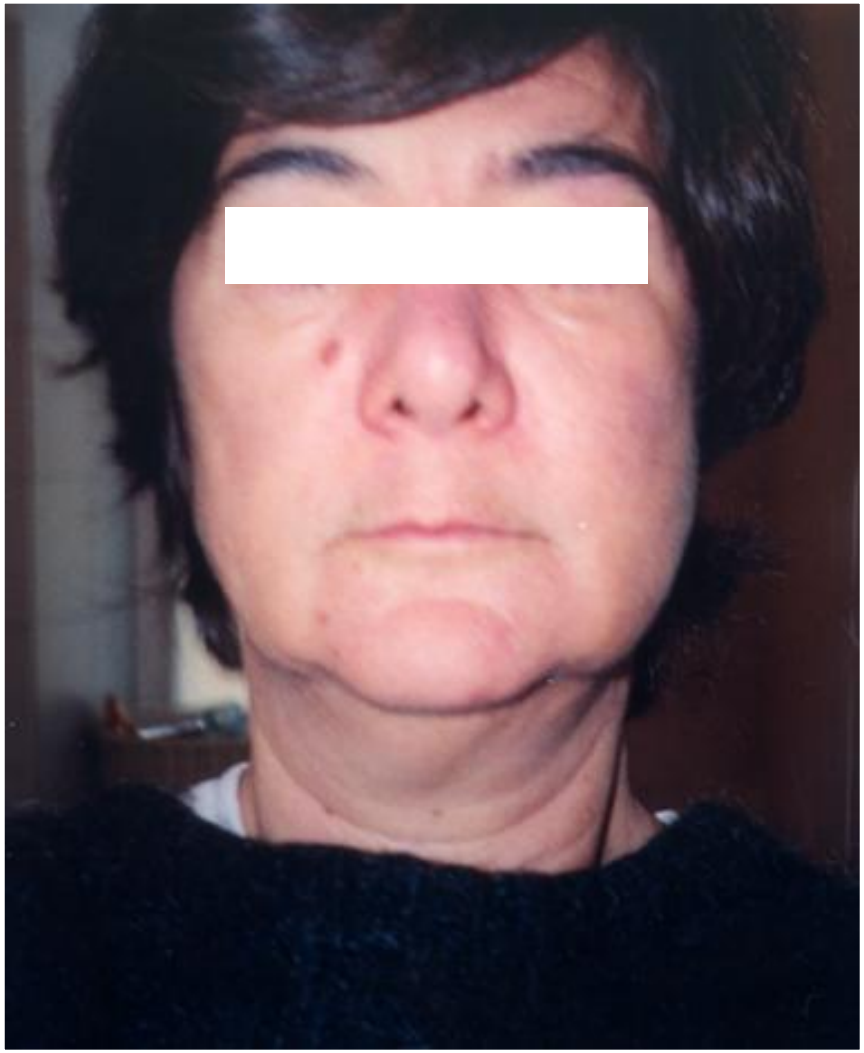
Il tessuto sottocutaneo

Angioedema cutaneo

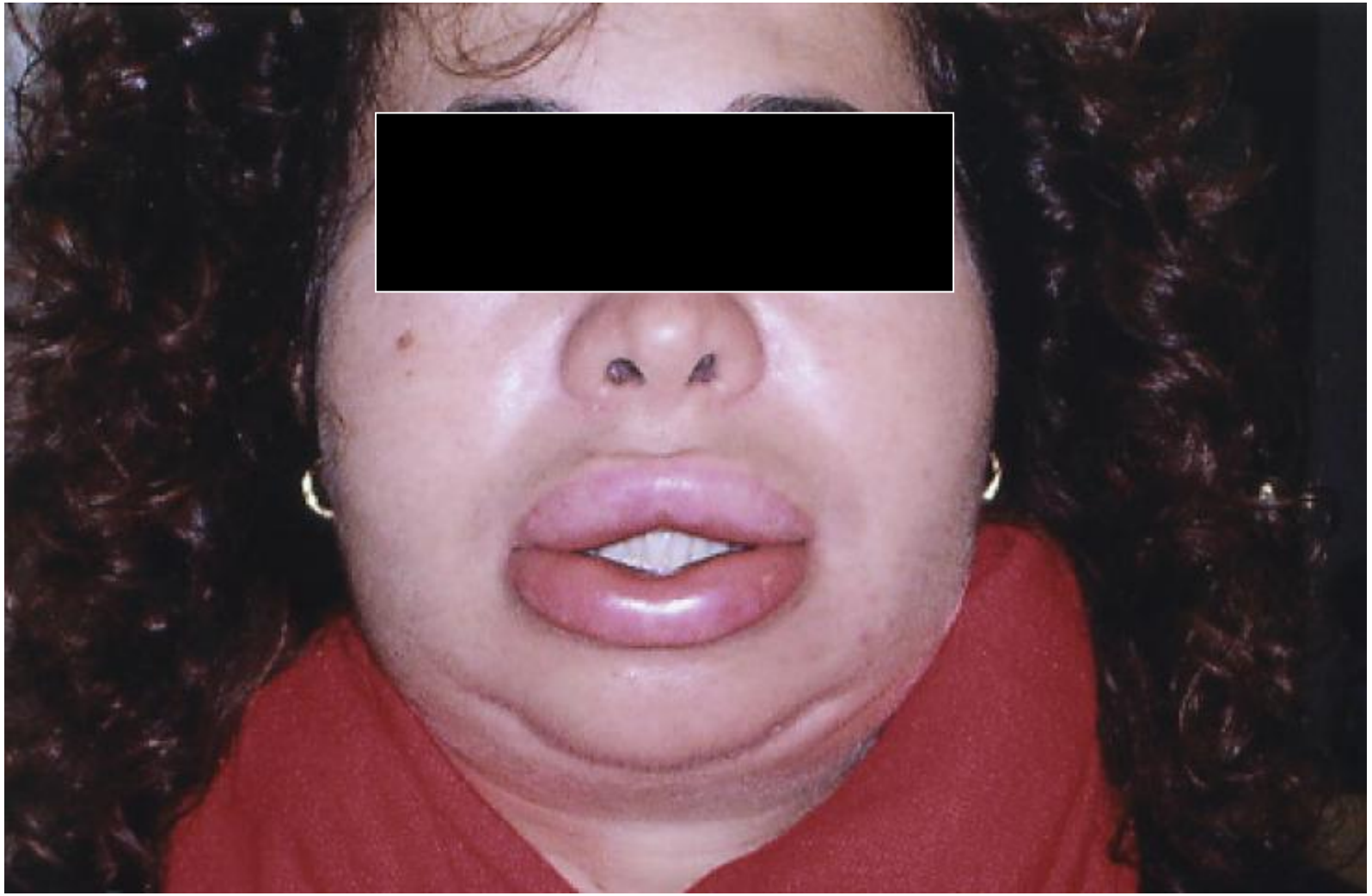


Angioedema facciale

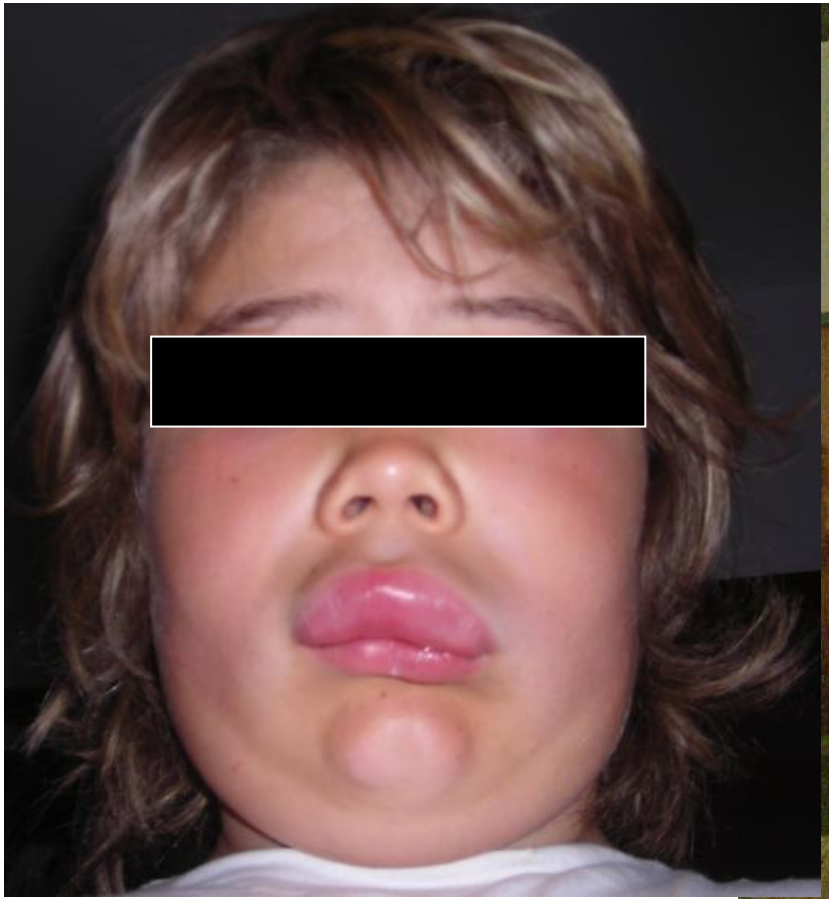


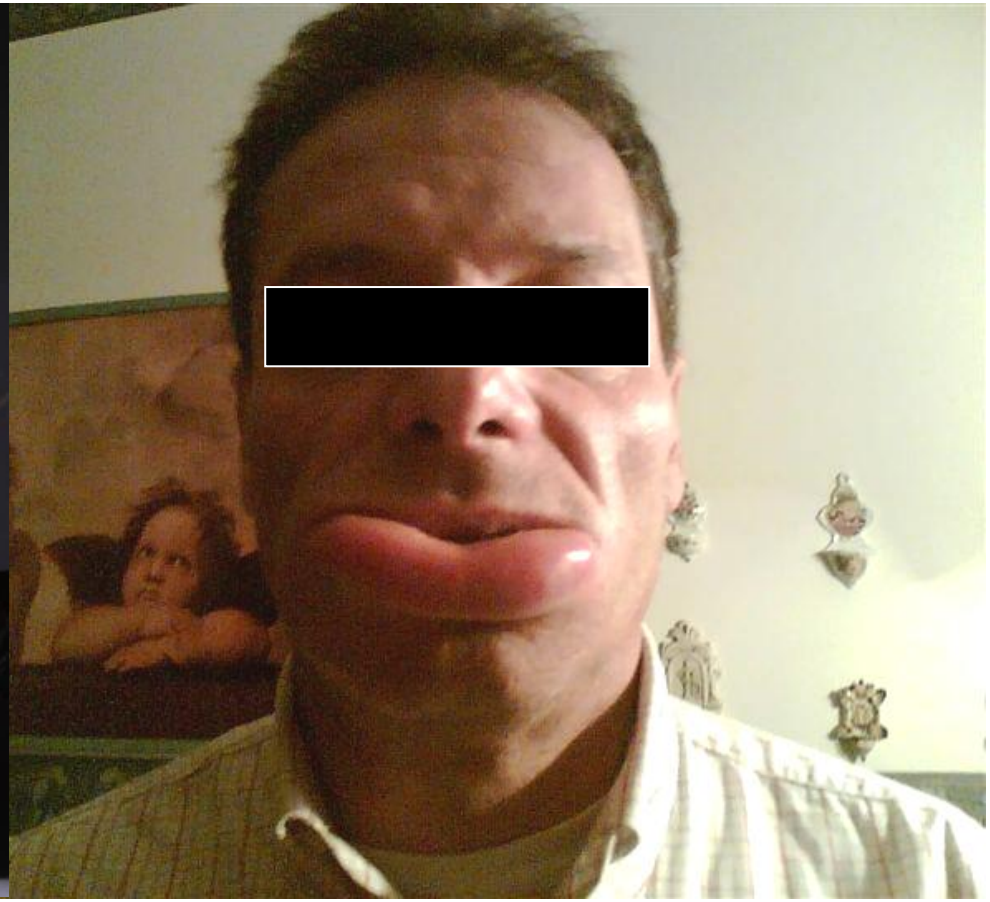


Angioedema delle labbra e volto



Angioedema del labbro





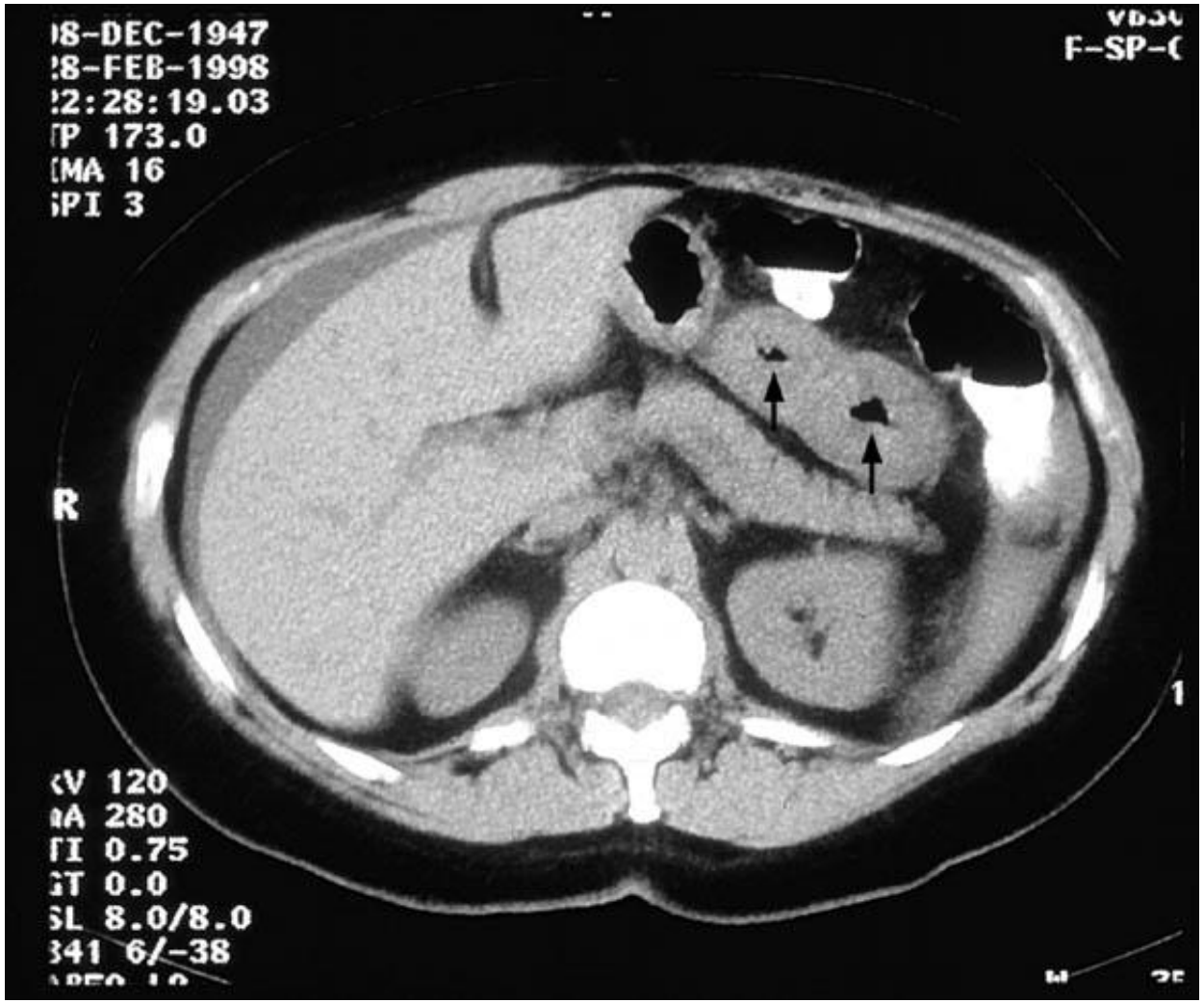
Quadro Clinico

- Le manifestazioni cliniche sono caratterizzate da **angioedemi** recidivanti non flogistici e non pruriginosi, autolimitantesi, durano mediamente 3-4 giorni, che possono interessare:

Il tessuto sottocutaneo

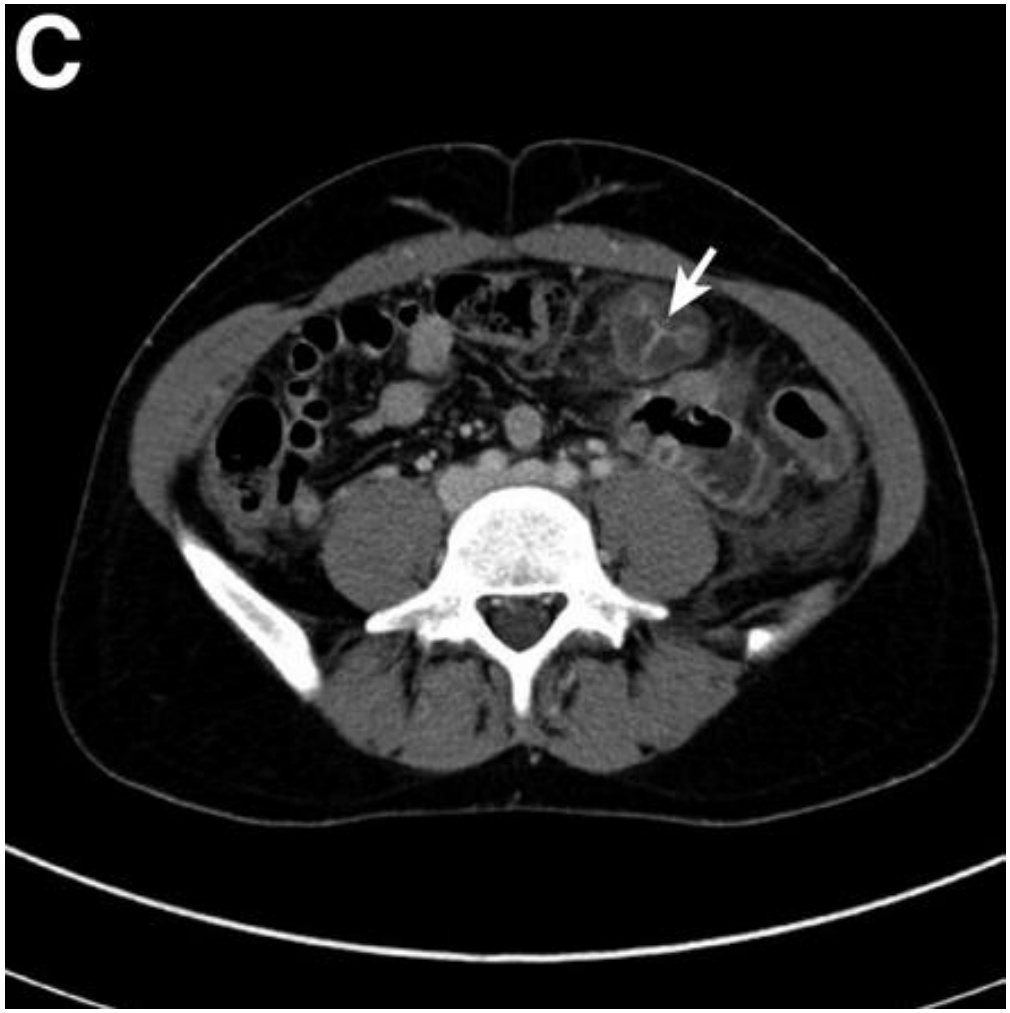
Il tessuto mucoso intestinale

Angioedema della mucosa intestinale



Wong et al. Gastroenterology 1999

Angioedema della mucosa intestinale

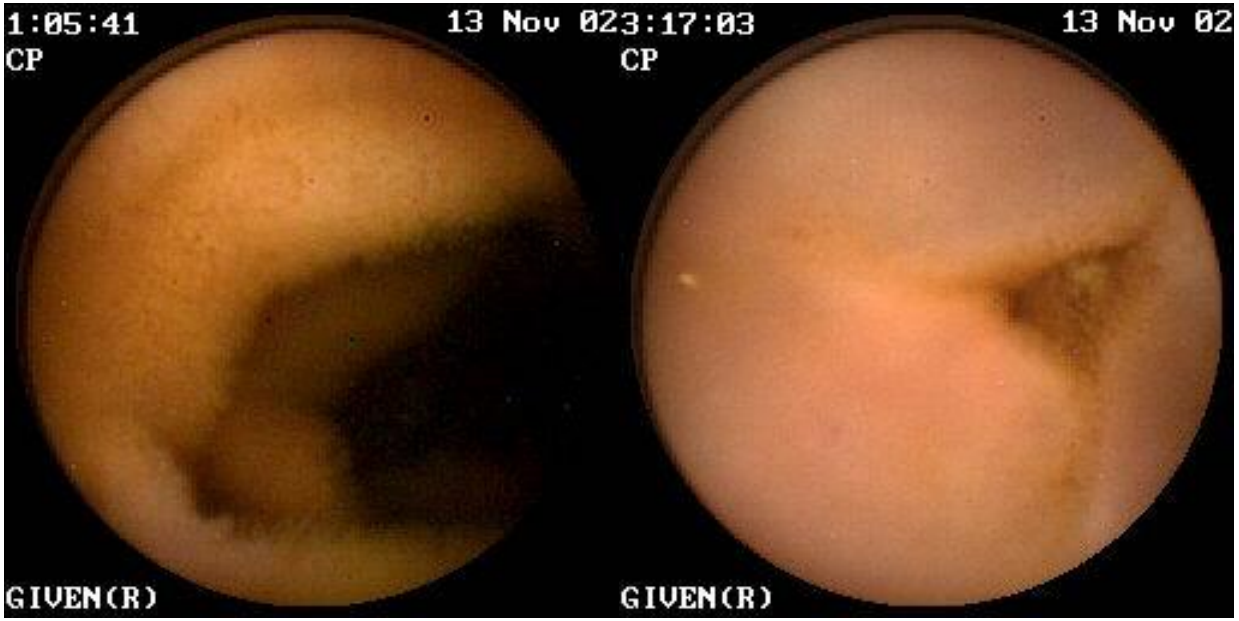


Cancian et al., *Gastroenterology*, 2011

Ileoscopia con capsula in corso di attacco di AE addominale

15:45

17:57

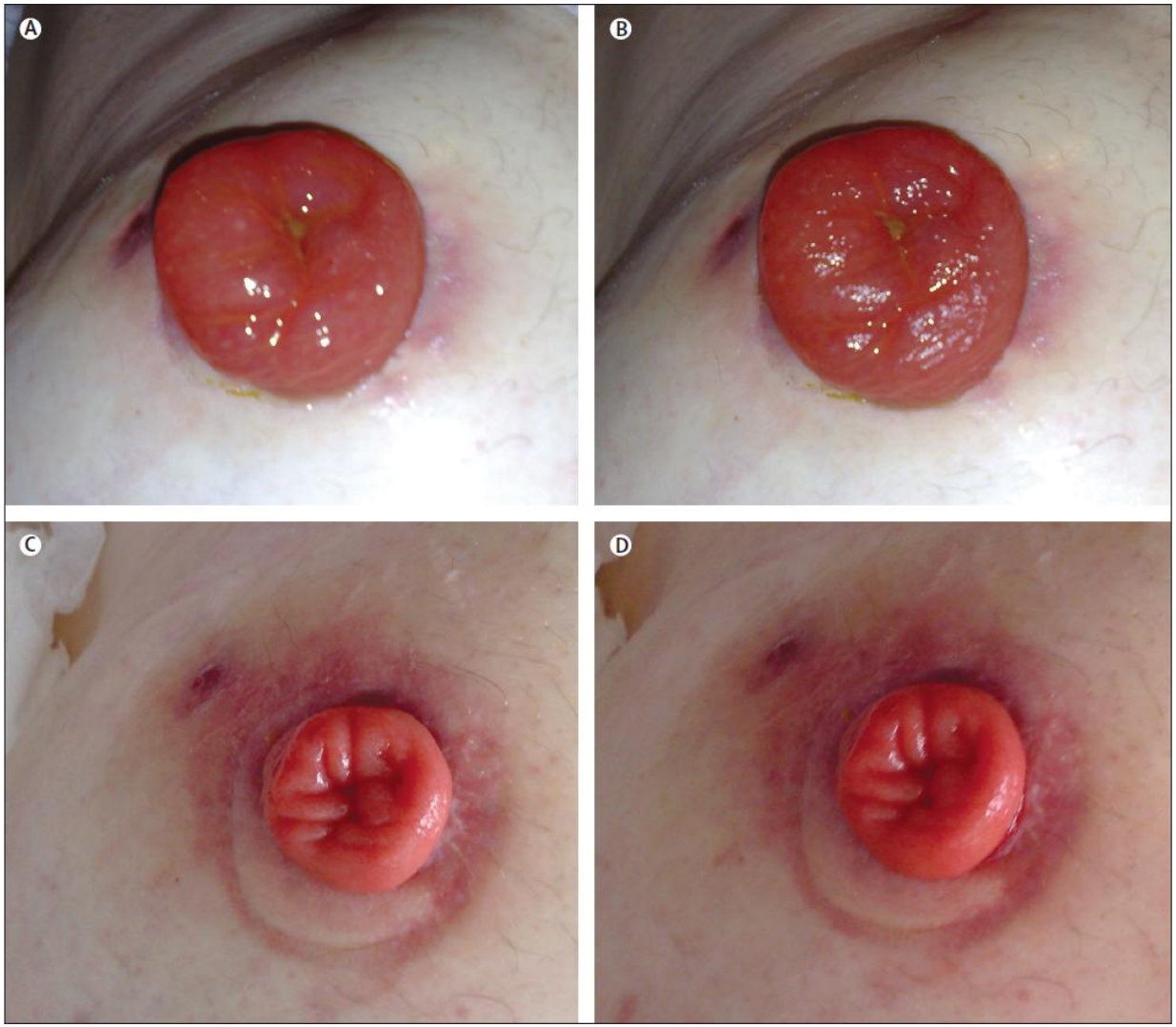


Ileo normale

Ileo con edema

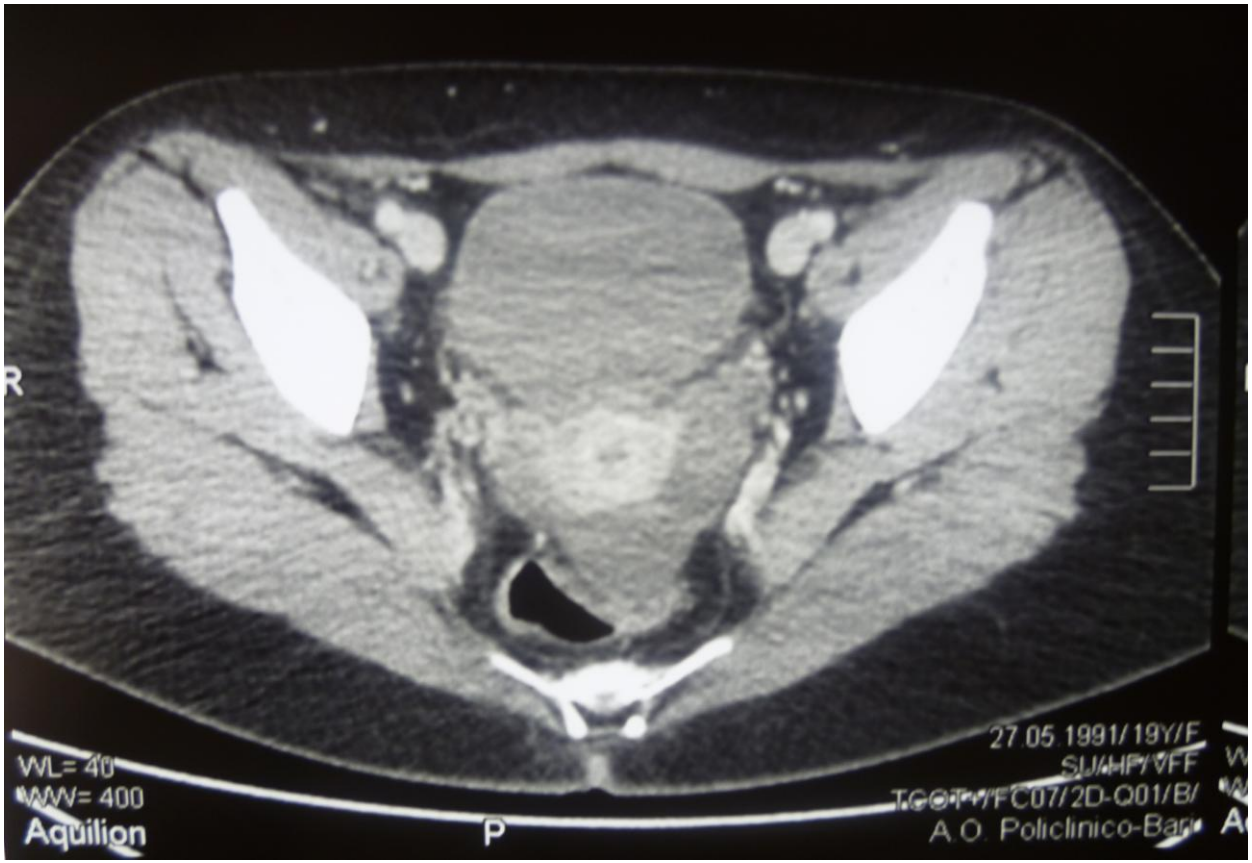
Cicardi, casistica personale

Edema della mucosa in colostomia

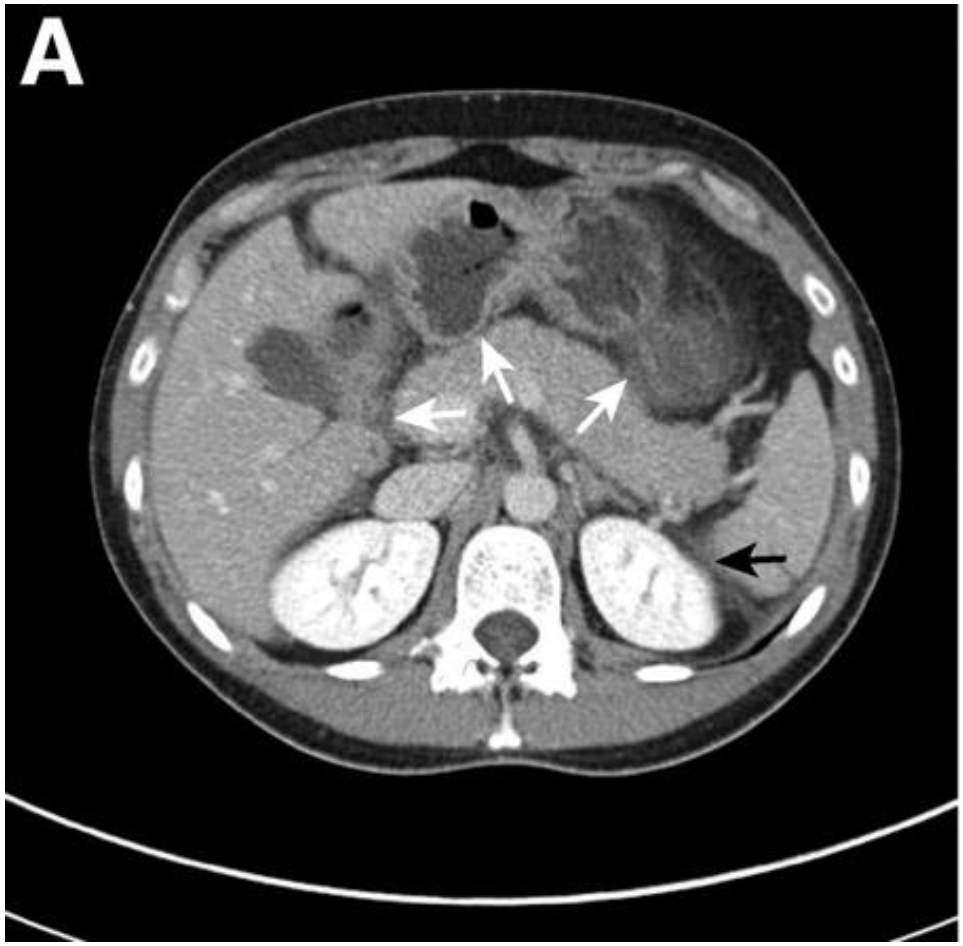


Farkas, Csuka; *Lancet* 2013; 381:1404

Versamento addominale nel Douglas

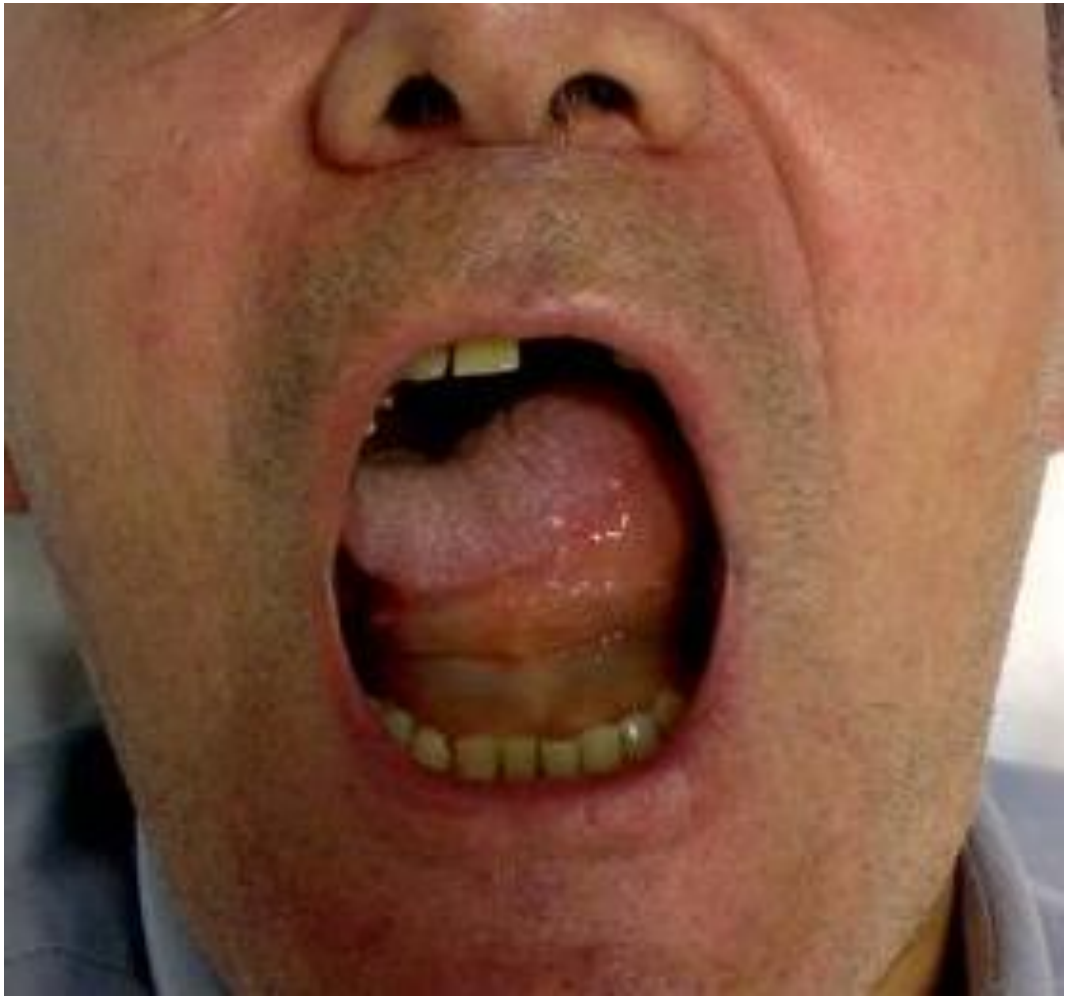


Pancreatite acuta in paz. con Angioedema ereditario



Cancian et al., *Gastroenterology*, 2011

Angioedema della lingua

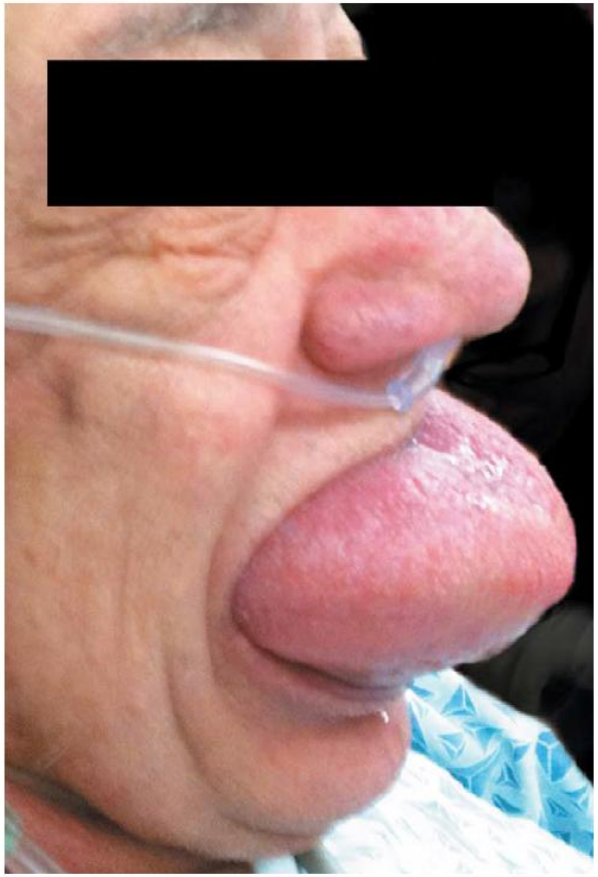


Edema della lingua

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Angioedema



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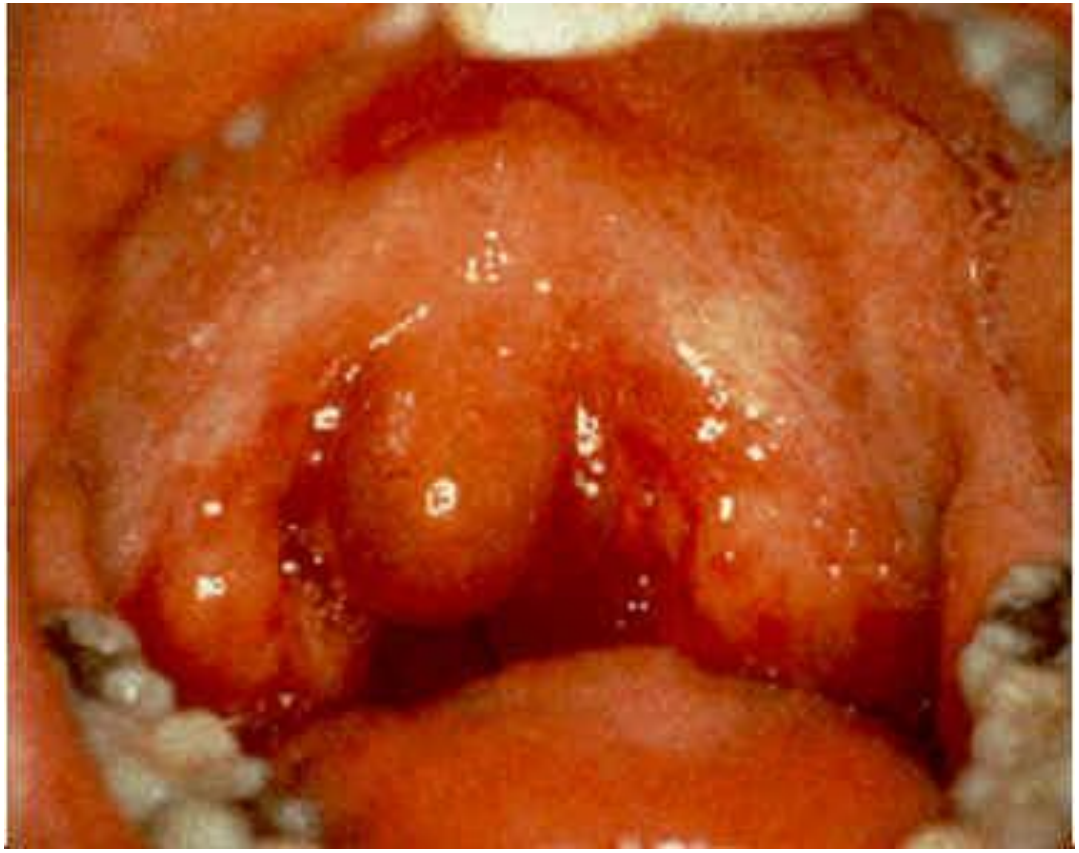
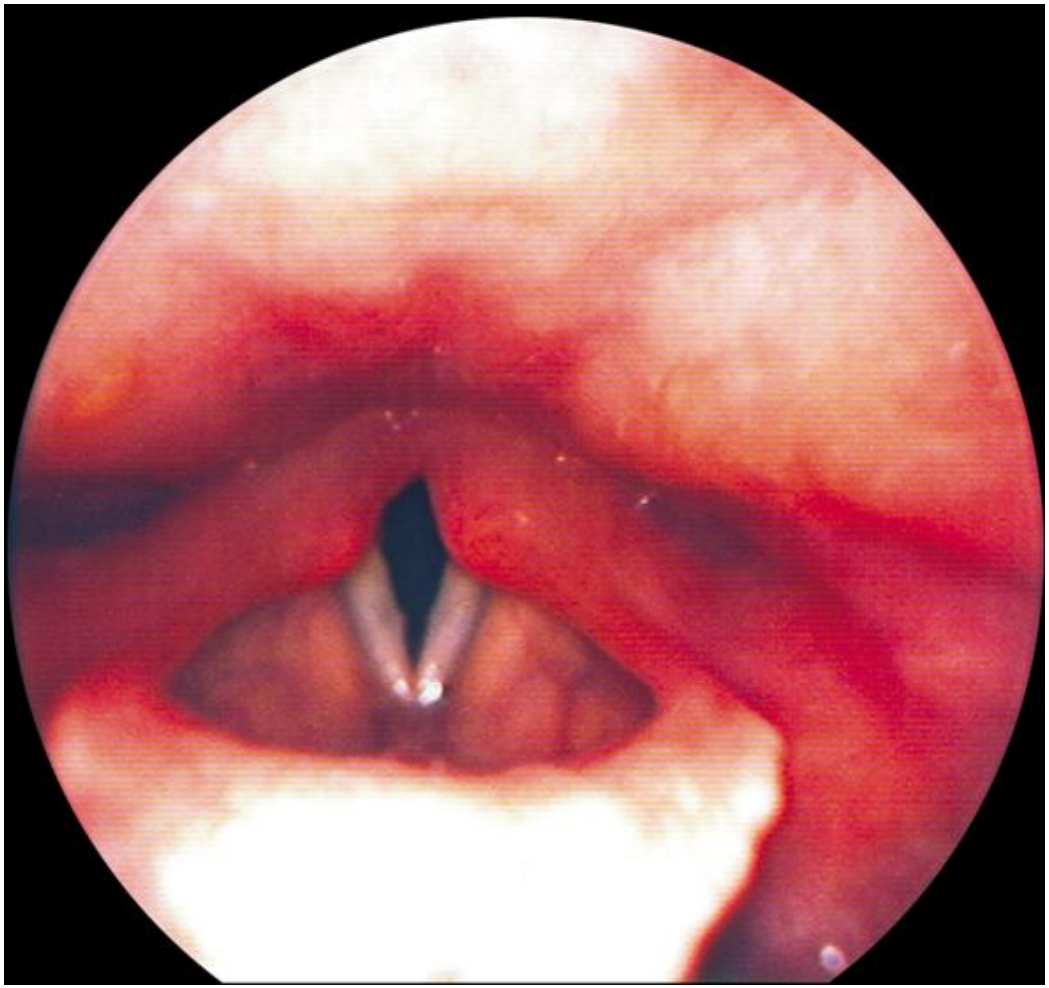
rbramante@nshs.edu

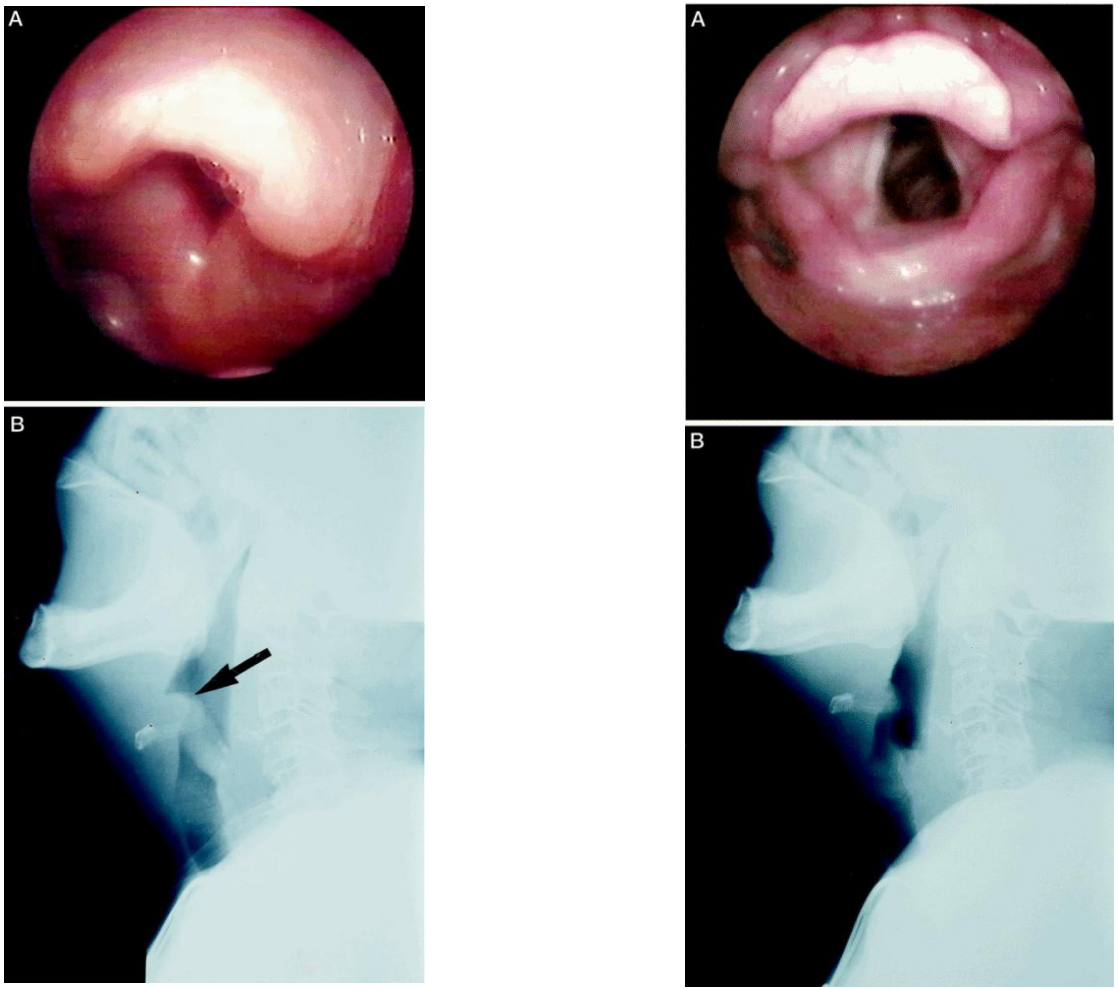
Edema Oro-fangieo



Edema laringeo



Laringoscopia durante un attacco di edema laringeo



Tsunoda et al. Laryngoscope 2000

Attacco di Angioedema - Laboratorio

- Emocromo: leucocitosi
- Segni biochimici di emoconcentrazione (↑ Hct, Prot. Tot.)
- Aumento PCR e D-Dimeri

Trattamento degli attacchi acuti

Angioedema ereditario

Obiettivi del trattamento

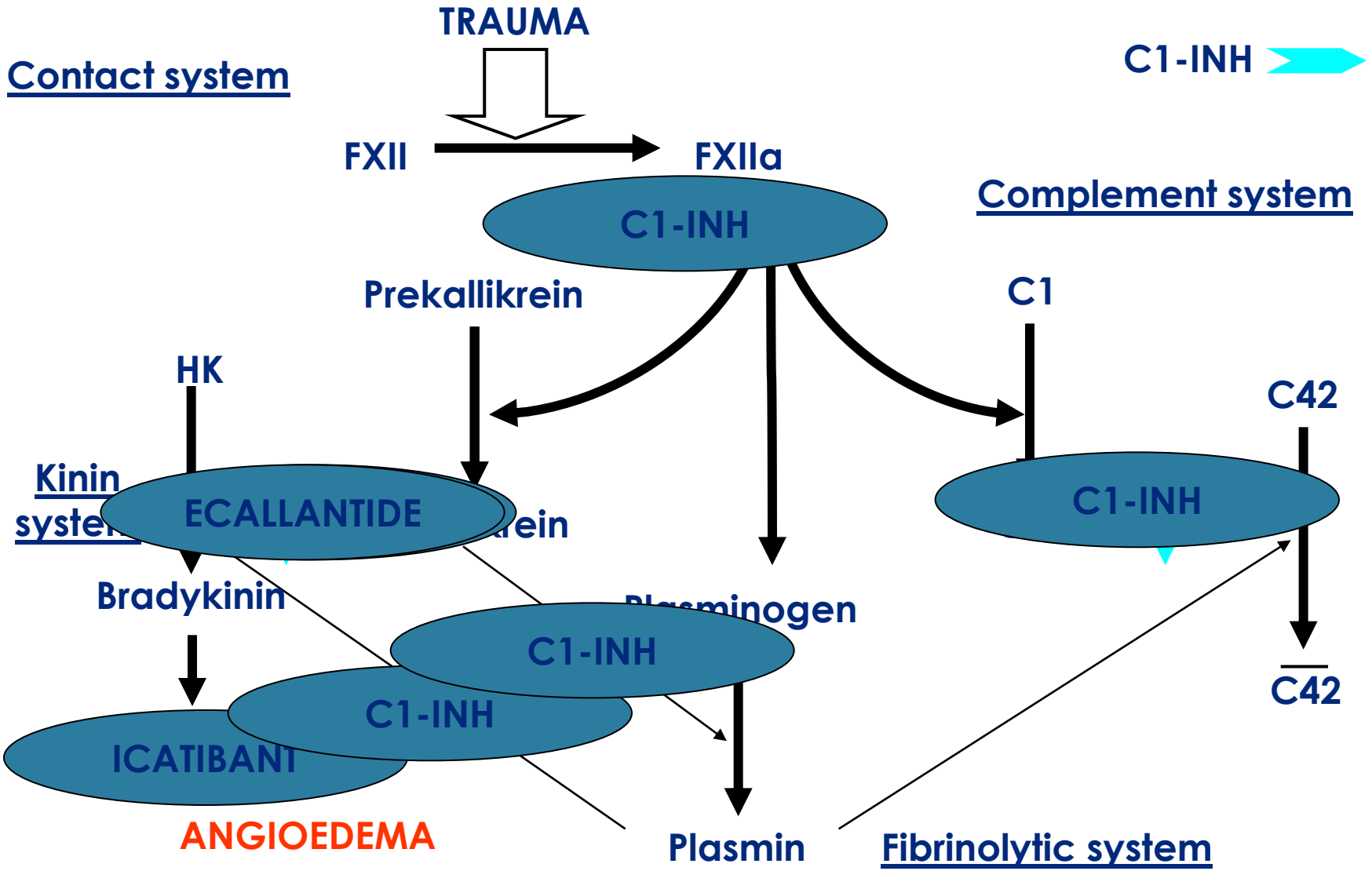
- Risolvere un attacco acuto quanto più rapidamente possibile
- Ridurre/Eliminare la mortalità (Edemi della glottide)
- Ridurre il disagio derivante dagli attacchi acuti e i giorni di inabilità
- Migliorare la qualità di vita dei pazienti affetti da Angioedema ereditario

Farmaci disponibili per gli attacchi acuti di angioedema

- C1 INH derivato plasmatico (pC1 INH)
  - Berinert
  - Cinryze
  - Cetor*
- C1 INH umano ricombinante
  - Ruconest
- Antagonista recettoriale della bradichinina (B2)
  - Firazyr (Icatibant)
- Inibitore della Callicreina
  - Kalbitor (Ecallantide)*

* Non disponibili in Italia

Farmaci per il trattamento degli attacchi di angioedema - Farmacodinamica



Caratteristiche del Pd-C1 INH (Berinert)

Fonte: plasma ottenuto da donatori controllati

Purificazione: crioprecipitazione, cromatografia a scambio ionico, precipitazione in glicole polietilene

Sicurezza: Donatori controllati

Test antivirali, sierologici e PCR

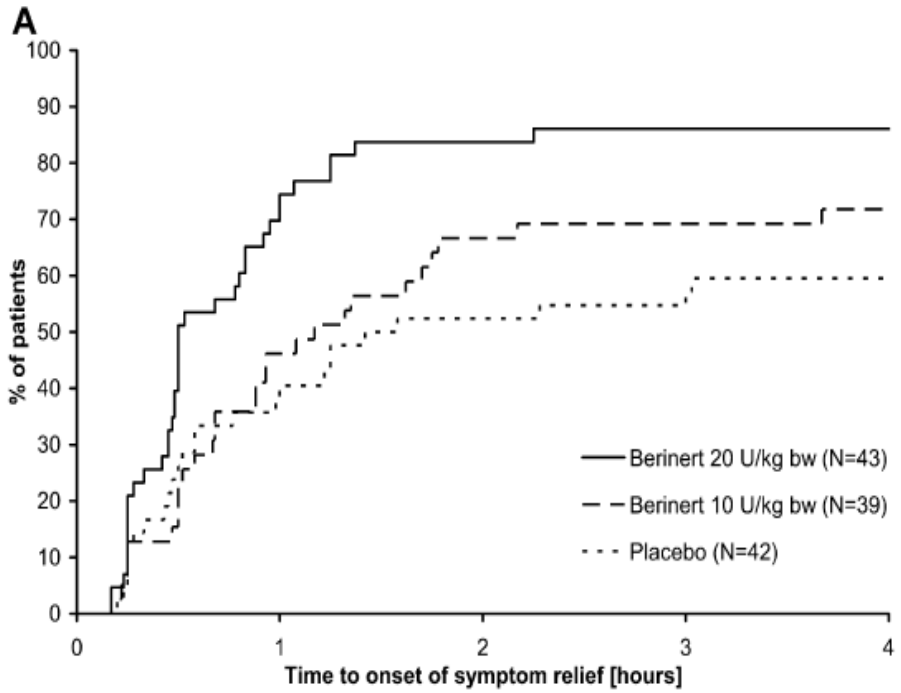
Inattivazione virale, pastorizzazione, cromatografia

Oltre 300.000 trattamenti senza alcun caso di siero-conversione per HIV, epatite B o C

J Allergy Clin Immunol 2004

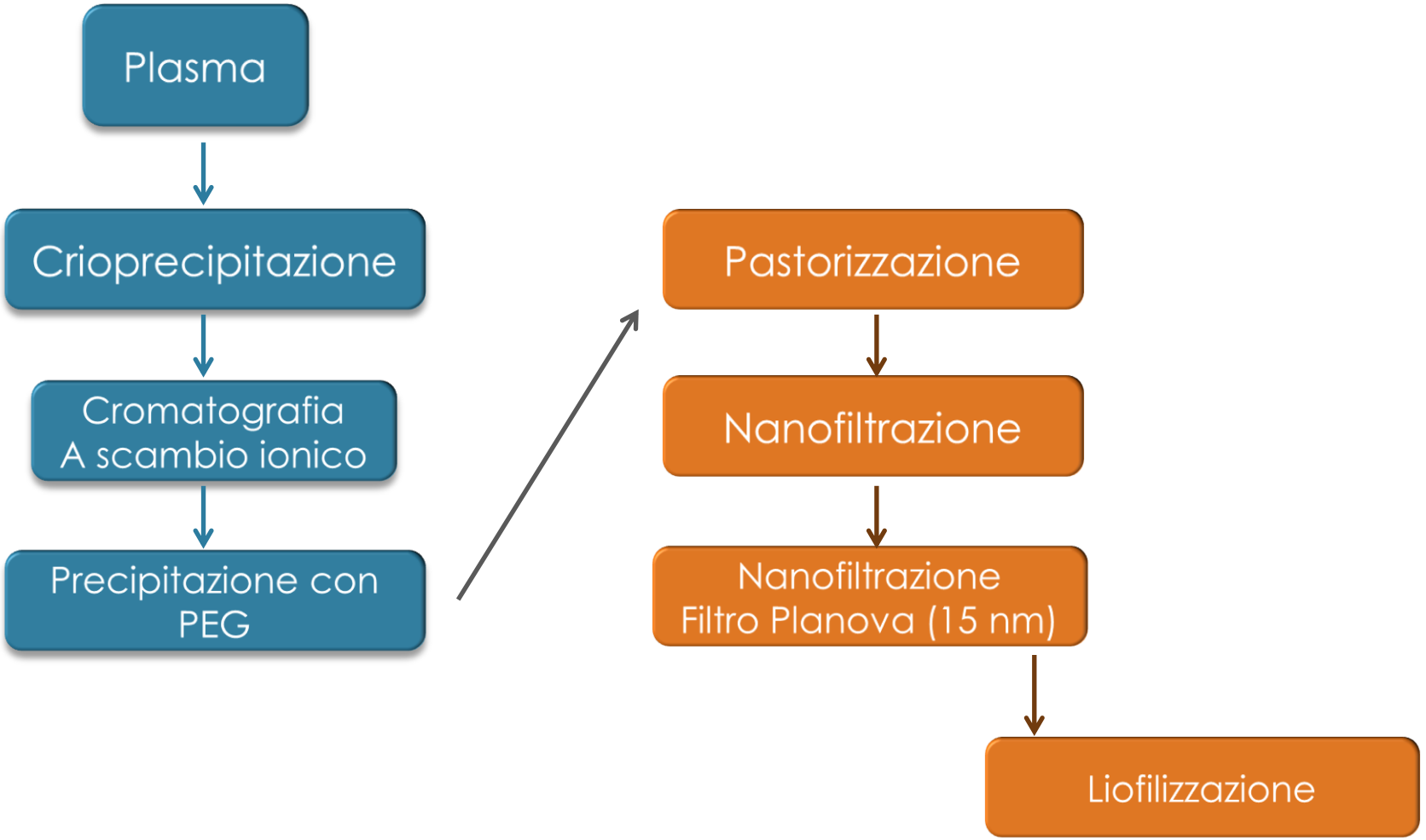
Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks

Timothy J. Craig, MD,[a] Robyn J. Levy, MD,[b] Richard L. Wasserman, PhD, MD,[c] Againdra K. Bewtra, MD,[d] David Hurewitz, MD,[e] Krystyna Obtułowicz, MD,[f] Avner Reshef, MD,[g] Bruce Ritchie, MD,[h] Dumitru Moldovan, MD,[i] Todor Shirov, MD,[j] Vesna Grivcheva-Panovska, MD,[k] Peter C. Kiessling, PhD,[l] Heinz-Otto Keinecke, MS,[m] and Jonathan A. Bernstein, MD[n] *Hershey, Pa, Atlanta, Ga, Dallas, Tex, Omaha, Neb, Tulsa, Okla, Krakow, Poland, Tel Hashomer, Israel, Edmonton, Alberta, Canada, Tirgu Mures, Romania, Sofia, Bulgaria, Skopje, Republic of Macedonia, Marburg, Germany, and Cincinnati, Ohio*



J Allergy Clin Immunol 2009, 124:801-9

C1 inibitore (Cinryze) - Preparazione



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 5, 2010 VOL. 363 NO. 6

Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema

Bruce L. Zuraw, M.D., Paula J. Busse, M.D., Martha White, M.D., Joshua Jacobs, M.D., William Lumry, M.D., James Baker, M.D., Timothy Craig, D.O., J. Andrew Grant, M.D., David Hurewitz, M.D., Leonard Bielory, M.D., William. E. Cartwright, M.D., Majed Koleilat, M.D., Walter Ryan, D.O., Oren Schaefer, M.D., Michael Manning, M.D., Pragnesh Patel, M.D., Jonathan A. Bernstein, M.D., Roger A. Friedman, M.D., Robert Wilkinson, M.D., David Tanner, M.D., Gary Kohler, M.D., Glenne Gunther, M.D., Robyn Levy, M.D., James McClellan, M.D., Joseph Redhead, M.D., David Guss, M.D., Eugene Heyman, Ph.D., Brent A. Blumenstein, Ph.D., Ira Kalfus, M.D., and Michael M. Frank, M.D.

C1 INH (Cinryze) negli attacchi acuti

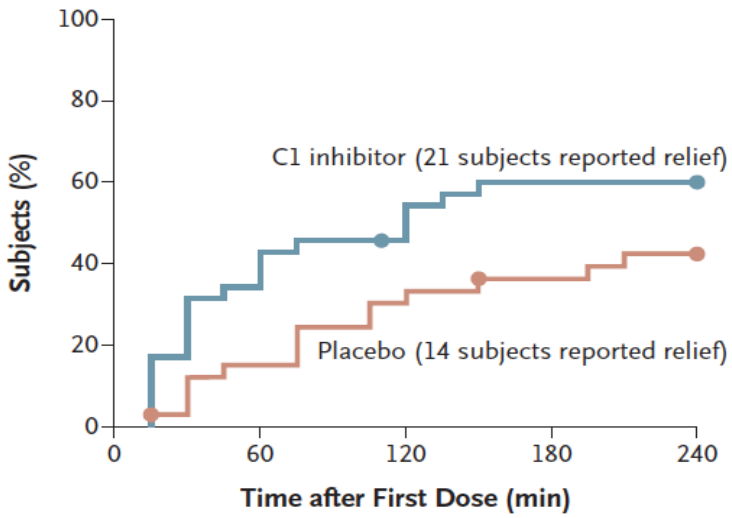


Figure 1. Primary Outcome in the Trial of C1 Inhibitor Therapy for Acute Attacks of Angioedema.

Cumulative incidence estimates for the time to the onset of unequivocal relief (primary outcome) are shown for 35 subjects who received nanofiltered C1 inhibitor concentrate and 33 subjects who received placebo. The circles represent either subjects who received rescue therapy before 4 hours (competing events; 2 subjects in the placebo group received narcotic rescue at 15 and 146 minutes, respectively, and 1 subject in the C1 inhibitor group received open-label C1 inhibitor rescue at 110 minutes) or those who did not have an onset of unequivocal relief before 4 hours.

- 71 Paz. Con età > 6 anni
  - 36 C1 INH, 35 placebo
- Somministrazione di 1000 U.I. o salina (doppio cieco)
- Rilevamento della intensità sintomi ogni 15 min
- Outcome: *Unequivocal relief (UR)* in 3 rilevazioni consecutive
- Tempo di comparsa di UR
  - C1 INH: 2 ore
  - Placebo: > 4 ore, p=0,02
- Tempo di risoluzione completa
  - C1 INH: 12,3 ore
  - Placebo: 25 ore, p= 0,004

Zuraw, *New Engl J Med*, 2010

Caratteristiche del Ruconest

Provenienza: latte da conigli transgenici per il C1 inibitore umano

Purificazione: scrematura del latte, cromatografia a scambio di cationi, inattivazione virale con incubazione con solventi/detergenti, cromatografia a scambio di anioni, cromatografia zinco-chelante, eliminazione dei virus con nanofiltrazione, ultrafiltrazione, filtrazione finale, liofilizzazione

Il rhC1-INH e il pdC1-INH differiscono per una diversa glicosilazione

J Allergy Clin Immunol September 2004

Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema

Bruce Zuraw, MD,[a]* Marco Cicardi, MD,[b]* Robyn J. Levy, MD,[c] Jan H. Nuijens, MD, PhD,[d] Anurag Relan, MD,[d]* Sonja Visscher,[d] Gerald Haase, MD,[e] Leonard Kaufman, PhD,[f] and C. Erik Hack, MD, PhD[g] *La Jolla, Calif, Milan, Italy, Atlanta, Ga, Leiden and Utrecht, The Netherlands, London, United Kingdom, and Brussels, Belgium*

J Allergy Clin Immunol 2010, 126:821-7

Pazienti: > 16 anni

Attacco acuto < 5 ore

VAS basale > 50 mm (0 mm: no sintomi, 100 mm: estremamente disabilitante)

Pazienti arruolati in Europa e Stati Uniti

Doppio cieco: 100 UI/Kg, 50 UI/Kg (USA), Salina

TABLE II. Primary and secondary efficacy outcome in the 3 treatment groups

Efficacy outcomes	rhC1INH 100 U/kg (N = 29)	rhC1INH 50 U/kg (N = 12)	Saline (N = 29)
Time to beginning of relief of symptoms (min)			
Median (95% CI)	66 (61-122)	122 (72-136)	495 (245-520)
Hazard ratio (95% CI) against saline	3.26 (1.85-5.74)	2.68 (1.23-5.85)	NA
Cox PH *P* value	<.001	.013	NA
Time to minimal symptoms (min)			
Median (95% CI)	266 (242-490)	247 (243-484)	1210 (970-1500)
Hazard ratio (95% CI) against saline	2.62 (1.48-4.61)	3.86 (1.71-8.72)	NA
Cox PH *P* value	<.001	.001	NA

NA, Not applicable.

The hazard ratios and Cox PH *P* value were calculated from a Cox PH model with treatment and study included as factors.

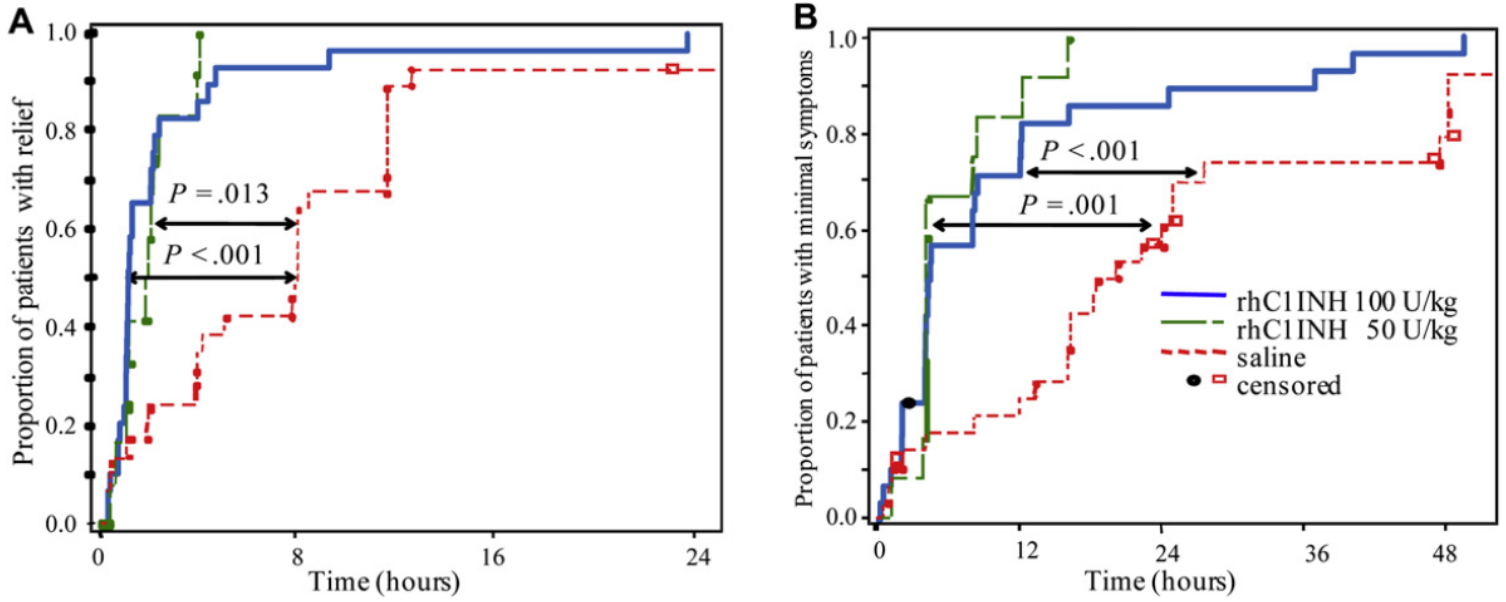
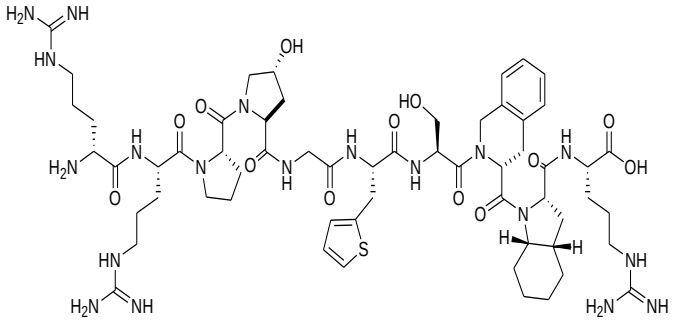


FIG 3. Kaplan-Meier plot of time (minutes) from start of infusion to the beginning of relief of symptoms **(A)** or of minimal symptoms **(B)**. Patients, who did not have beginning of relief of symptoms or minimal symptoms during the observation period, were censored at the time the last overall VAS score was recorded (indicated with a *tag*). One patient of the saline group with censored onset of relief >2000 minutes is not indicated in the graph. Modified with permission from Frank MM, Recombinant and plasma-purified human C1 inhibitor for the treatment of hereditary angioedema, p S31. In: New perspectives in hereditary angioedema (HAE): molecular mechanisms & therapeutic choices. *World Allergy Organization Journal* 2010 Supplement;3(9):s29-40.

Farmaci che bloccano l'azione della bradichinina o della callicreina

Prodotto	Provenienza	Meccanismo d'azione	Somministrazione	Indicazione
Dx-88/ Ecallantide (Kalbitor®)	Proteina ricombinante	Inibitore callicreina	Sottocutanea	Emergenza On demand
Icatibant (Firazyr®)	Peptide di sintesi	Antagonista recettore B2 bradichinina	Sottocutanea	Emergenza On demand

Caratteristiche dell'icatibant



Icatibant H-**D-Arg**-Arg-Pro-**Hyp**-Gly-**Thi**-Ser-**D-Tic-Oic**-Arg-OH
(10mer)

Bradykinin H-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH
(9mer)

- Decapeptide sintetico, non di derivazione plasmatica, con alta specificità e affinità per il recettore B2 della bradichinina (non interazioni con altri recettori)
- Struttura simile alla bradichinina ma contiene 5 amino acidi non-proteinogenici (D-Arg, L-Hyp, L-Thi, D-Tic, and L-Oic)
- Stabile e non degradato dagli enzimi che clivano la bradichinina come la carbossipeptidasi N e l'enzima di conversione dell'angiotensina (ACE)
- Emivita plasmatica: 2,3 h

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema

M. Cicardi, A. Banerji, F. Bracho, A. Malbrán, B. Rosenkranz, M. Riedl, K. Bork, W. Lumry, W. Aberer, H. Bier, M. Bas, J. Greve, T.K. Hoffmann, H. Farkas, A. Reshef, B. Ritchie, W. Yang, J. Grabbe, S. Kivity, W. Kreuz, R.J. Levy, T. Luger, K. Obtulowicz, P. Schmid-Grendelmeier, C. Bull, B. Sitkauskiene, W.B. Smith, E. Toubi, S. Werner, S. Anné, J. Björkander, L. Bouillet, E. Cillari, D. Hurewitz, K.W. Jacobson, C.H. Katelaris, M. Maurer, H. Merk, J.A. Bernstein, C. Feighery, B. Floccard, G. Gleich, J. Hébert, M. Kaatz, P. Keith, C.H. Kirkpatrick, D. Langton, L. Martin, C. Pichler, D. Resnick, D. Wombolt, D.S. Fernández Romero, A. Zanichelli, F. Arcoleo, J. Knolle, I. Kravec, L. Dong, J. Zimmermann, K. Rosen, and W.-T. Fan*

N Engl J Med 2010;363:532-41.

Clinical Outcomes in the FAST-1 and FAST-2 Trials, According to Study Group

Table 2. Clinical Outcomes in the FAST-1 and FAST-2 Trials, According to Study Group.*

Outcome	FAST-1			FAST-2		
	Icatibant (N=27)	Placebo (N=29)	P Value	Icatibant (N=36)	Tranexamic Acid (N=38)	P Value
Time to clinically significant relief of the index symptom (primary end point) — hr			0.14			<0.001
Median	2.5	4.6		2.0	12.0	
IQR	1.1–6.0	1.8–10.2		1.0–3.5	3.5–25.4	
Time to first symptom improvement — hr						
According to patient			<0.001			<0.001
Median	0.8	16.9		0.8	7.9	
IQR	0.5–2.0	3.2–NA		0.4–1.4	1.1–NA	
According to investigator			<0.001			<0.001
Median	1.0	5.7		1.5	6.9	
IQR	0.8–2.0	2.0–11.2		0.7–3.0	4.0–13.8	
Time to almost complete relief of symptoms — hr			0.08			<0.001
Median	8.5	19.4		10.0	51.0	
IQR	2.5–31.5	10.2–55.7		2.8–23.2	12.0–79.5	
Clinically significant relief of the index symptom at 4 hr after start of study drug — % (95% CI)	67 (46–84)	46 (28–66)†	0.18	80 (63–92)†	31 (16–48)‡	<0.001

* NA denotes not available, CI confidence interval, and IQR interquartile range.
† Data are missing for one patient.
‡ Data are missing for two patients.

Cicardi M et al. N Engl J Med 2010;363:532-541

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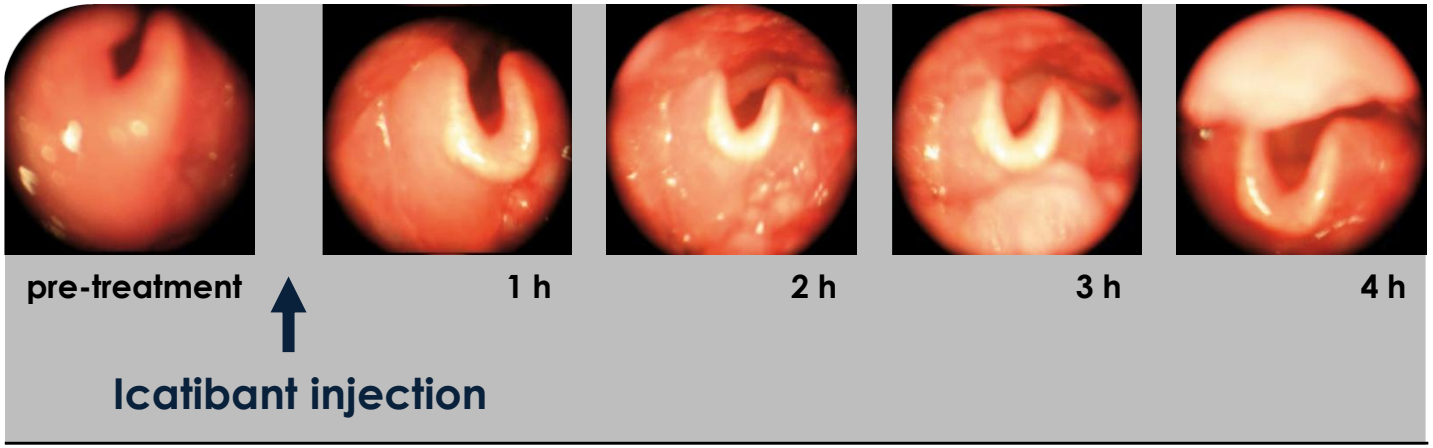
Icatibant nell'edema laringeo



Farmaci per l'attacco acuto di angioedema – Situazioni particolari

	pdC1 INH	rhC1 INH	Icatibant
Pazienti pediatrici (< 18 anni)	+	-	-
Gravidanza/Allattamento	+	-	-
Allergie a coniglio	+	-	+
Coronaropatia	+	+	-
Difficoltà accesso venoso	-	-	+

Linee Guida – Trattamento acuto

Angioedema ereditario

Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI
Allergy

REVIEW ARTICLE

Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group

M. Cicardi[1], K. Bork[2], T. Caballero[3], T. Craig[4], H. H. Li[5], H. Longhurst[6], A. Reshef[7] & B. Zuraw[8] on behalf of HAWK* (**H**ereditary **A**ngioedema International **W**or**k**ing Group)

[1]Dipartimento di Scienze Cliniche ''Luigi Sacco'', Università di Milano, Ospedale L. Sacco, Milano, Italy; [2]Department of Dermatology, Johannes Gutenberg University, Mainz, Germany; [3]Servicio de Alergia, Hospital Universitario La Paz, Health Research Institute, IdiPaz, Madrid, Spain; [4]Departments of Medicine and Pediatrics, Penn State University, Hershey, PA; [5]Institute for Asthma and Allergy, Wheaton, MD, USA; [6]Barts and the London NHS Trust, London, UK; [7]Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel; [8]University of California, San Diego, CA, USA

To cite this article: Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, Reshef A, Zuraw B on behalf of HAWK (**H**ereditary **A**ngioedema International **W**or**k**ing Group). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2011; DOI: 10.1111/j.1398-9995.2011.02751.x.

Obiettivi del trattamento

1. Reducing morbidity and mortality in HAE must begin with early and accurate diagnosis.
2. HAE patients should have a specialist familiar with the disease involved in their care.
3. Treatment for HAE must be individualized to patient's needs and request to provide optimal care and restore a normal quality of life to the patient.

HAKW Guidelines: Cicardi et al., *Allergy* 2012; **67**: 147–157.

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Accesso ai farmaci

9. Any angioedema attack in HAE patients can become disabling and/or life-threatening: therefore, all patients with HAE owing to C1-INH deficiency, even if still asymptomatic, should have access to at least one of the specific medicines, plasma-derived and recombinant C1-INHs, icatibant, and ecallantide, which obtained high grade of evidence from the above-mentioned trial for their efficacy in treating acute attacks 'on demand'.

HAKW Guidelines: Cicardi et al., *Allergy* 2012; **67**: 147–157.

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Trattamento *on-demand* a domicilio

10. Whenever possible and allowed by drug-specific summary product characteristics, patients should have the on-demand medicine to treat acute attacks at home and should be trained to self-administer these medicines. This recommendation has a low level of evidence because it is based on observational studies showing higher efficacy of early on-demand home treatment *vs* hospital treatment for angioedema attacks (38, 39). Nevertheless, it is very unlikely that controlled studies will be organized to test the appropriateness of this recommendation whose level of evidence will be reinforced by large, prospective observational data.

HAKW Guidelines: Cicardi et al., *Allergy* 2012; **67**: 147–157.

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Trattare tutti gli attacchi di angioedema

11. All attacks, irrespective of location, are eligible for treatment as soon as they are clearly recognized by the patient, ideally before visible or disabling symptoms develop. This recommendation has high level of evidence provided by controlled studies (9–12), showing that all the medications tested in these studies for angioedema attacks shorten their duration and therefore the attack-related inability.

HAKW Guidelines: Cicardi et al., *Allergy* 2012; **67**: 147–157.

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Attacchi laringei

12. Patients should immediately report to the hospital if laryngeal symptoms persist following an initial treatment. This recommendation is based on clinical experience showing the unpredictability of the evolution of laryngeal edema. Testing this recommendation in controlled or observational studies seems clearly unethical.

HAKW Guidelines: Cicardi et al., *Allergy* 2012; **67**: 147–157.

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Attacco acuto HAE - Trattamento

- Trattare l'attacco all'inizio della sua evoluzione
- pdC1 INH
  - Berinert (Fiale da 500 U.I.): 20 U.I./Kg in bolo **e.v.** (no diluizione)
  - Cinryze (Fiale da 500 U.I.): 1.000 U.I. **e.v.** (no diluizione)
  - Eventuale ripetizione della dose in base alla risposta clinica dopo 2-3 ore (specie nelle forme laringee)
- rhC1 INH (Ruconest)
  - Fl. da 2100 U.I. (1-2 fl. **e.v.** in base al peso corporeo)
  - Trial clinico: 50 U.I./Kg p.c.
- Icatibant (Firazyr)
  - Fl. da 30 mg (1 fl. **s.c.** regione addominale, iniezione profonda e lenta), eventualmente ripetibile dopo 6 h (10% attacchi) e dopo 24h (2% attacchi)

A.A.E.E.

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e la terapia dell'angioedema ereditario - onlus

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Dott. Vincenzo Montinaro
Dott. Giuseppe Castellano
Dott.ssa Anna Zito
Dott.ssa Adele Mitrotti
Dott.ssa Grazia Pia Iaffaldano

Grazie per l'attenzione