The 24nd Word Allergy Congress

Seoul, Korea

14 October, 2014

Workshop 3: Recent Update in Chronic Urticaria

Wednesday, 14 October 2015: 13:30 - 15:00

13:35 - 13:55

Update in the Pathogenesis of Chronic Urticaria in Adults

Chair: Dr Chei-Soo (South Korea), Dr Jonathan Bernstein (US)

Workshop 3: Recent Update in Chronic Urticaria
Room 201 (Floor 2) (Coex Convention Center)
Chairpersons: *Chein-Soo Hong (South Korea) , Jonathan Bernstein (US)*

13:30 - 13:35	**Welcoming Remarks**
13:35 - 13:55	**3-1WS: Update in the Pathogenesis of Chronic Urticaria in Adults** | Michihiro Hide (Japan)
13:55 - 14:15	**3-2WS: Natural Course and Etiologic Factors of Chronic Urticaria in Children** | Orathai Piboonpocanun (Thailand)
14:15 - 14:35	**3-3WS: Efficacy and Therapeutic Monitoring of Anti-IgE Therapy in Chronic Refractory Urticaria** | Allen Kaplan (United States)
14:35 - 15:00	**Discussion**

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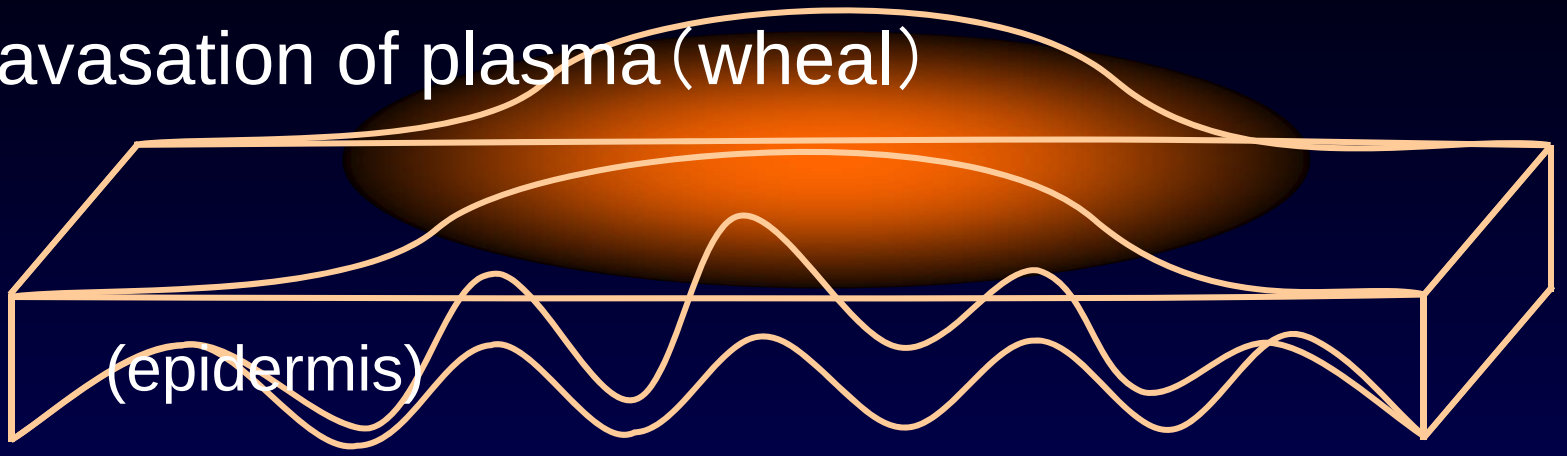
COI Disclosure

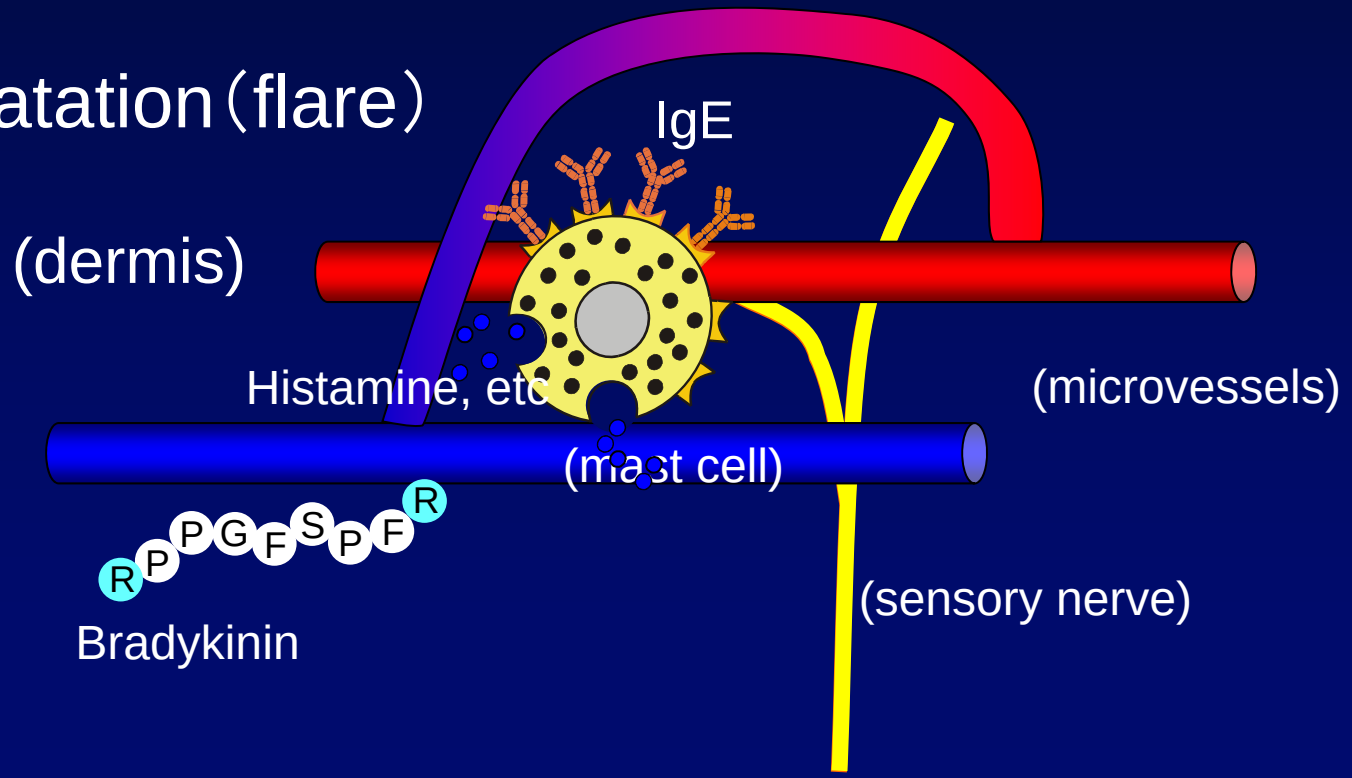
In relation to this presentation, I declare the following, real or perceived conflicts of interest:

Consultancy fees from
-MSD
-Novartis

Research support and Speaker's Bureau from
-GlaxoSmithKline
-Tanabe-Mitsubishi
-Kyouwahakkou-Kirin

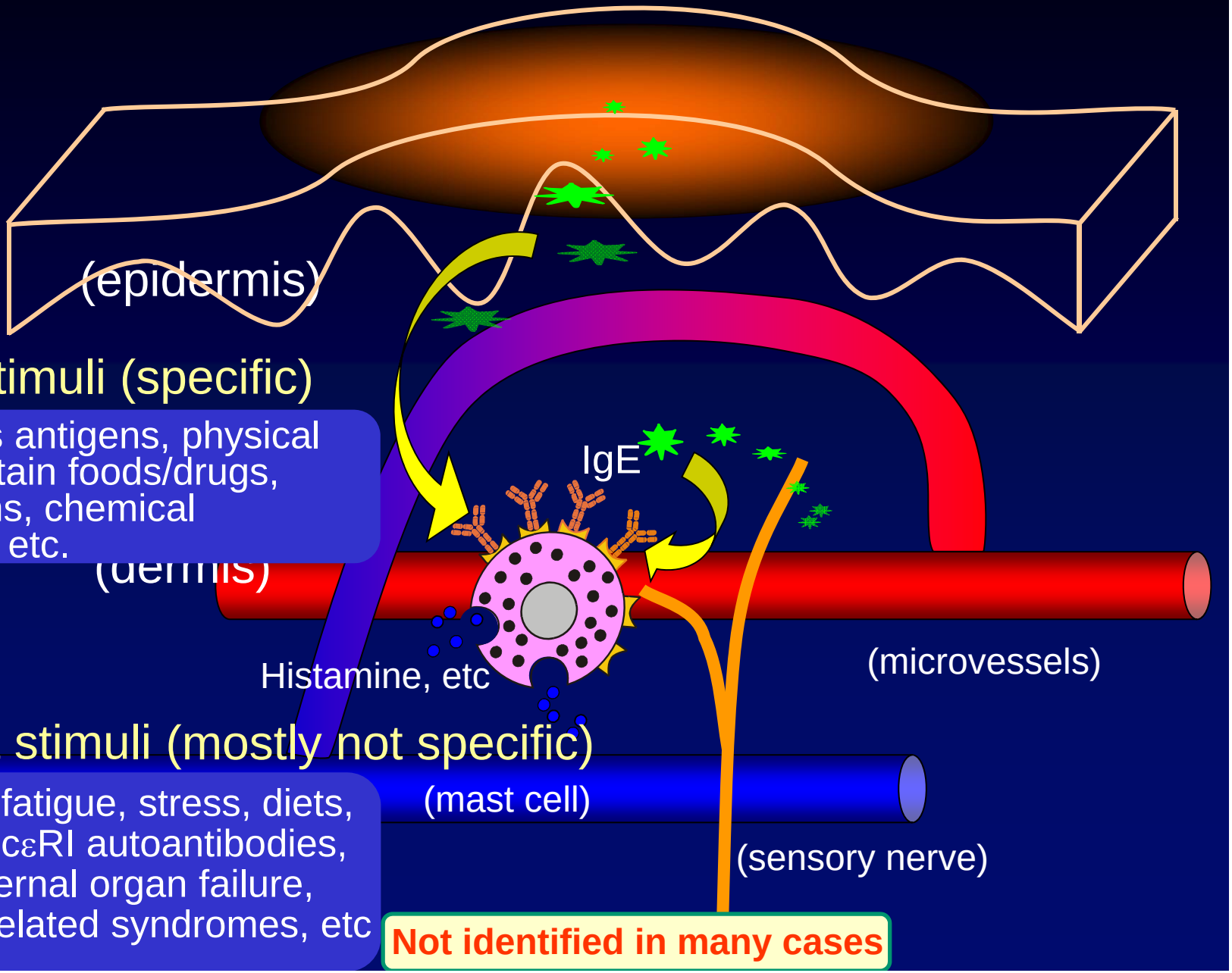
Urticaria is a disease that develops wheals





In spite of relatively simple clinical features, the shape and size of the eruptions and the etiology of urticaria is largely various and heterogeneous.

Urticaria is a disease that develops wheals



- direct stimuli (specific)

Exogenous antigens, physical stimuli, certain foods/drugs, insect toxins, chemical substance, etc.

- Indirect stimuli (mostly not specific)

Infection, fatigue, stress, diets, anti-IgE/FcεRI autoantibodies, drugs, internal organ failure, urticaria related syndromes, etc

Not identified in many cases

Classification of chronic urticaria subtypes (presenting with wheals, angioedema, or both)

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria (CSU)	Inducible Urticaria
Spontaneous appearance of wheals, angioedema, or both ≧6 weeks due to known or unknown causes	Symptomatic dermographism[1] Cold urticaria[2] Delayed pressure urticaria[3] Solar urticaria Heat urticaria[4] Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria
[1]also called urticaria factitia, dermographic urticaria; [2]also called cold contact urticaria, [3]also called pressure urticaria; [4]also called heat contact urticaria;	

Physical urticarias

*Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur as a symptom, for example skin prick test, anaphylaxis, auto-inflammatory syndromes, or hereditary angioedema (bradykinin-mediated angioedema).

Zuberbier T, et al. Allergy 69:868-887, 2014

Factors that may be associated with the pathogenesis of urticaria

1.Direct triggers（mainly exogenous and transient）

1) Exogenous antigens

2) Physical stimuli

3) Sweating

4) Foods*

food antigens, food histamine, pseudo-allergens (pork, bamboo shoot, rice cake, spices, etc), food additives (preservatives, artificial pigment), salicylic acids*

5) Drugs

antigens, contrast media, NSAIDs*, preservatives, succinic acid esters, vancomycin (red man syndrome), etc

6) Exercises

Any one is not sufficient to cause urticaria by itself

2.Backgound factors（mainly endogenous and continuous)

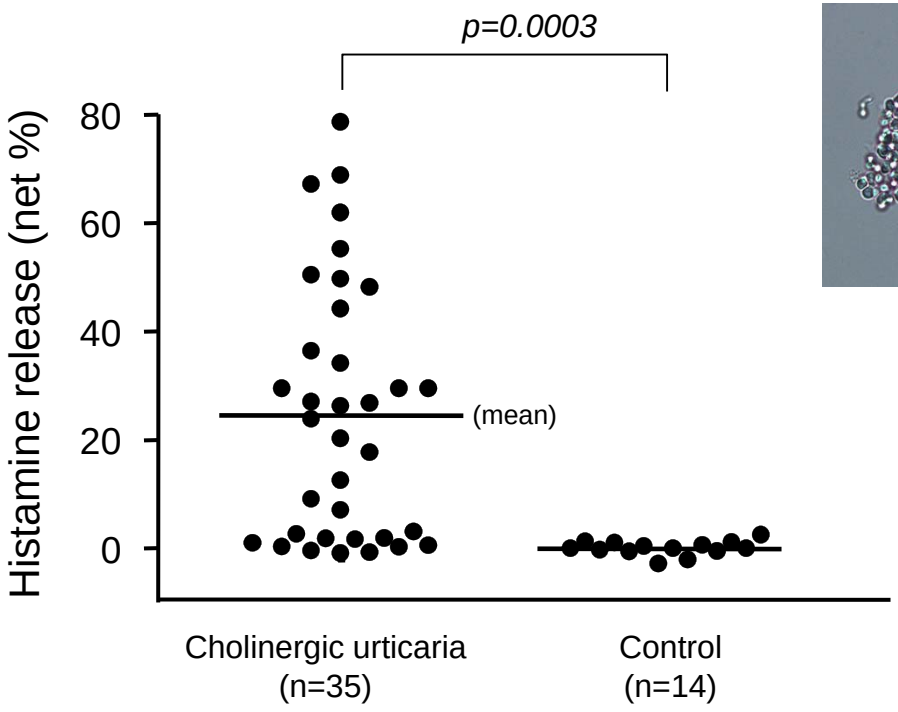
1) Sensitization（specific IgE）
2) Infections
3) Tiredness/stress
4) Foods*, except for antigens
5) Drugs: Aspirin*, other NSAIDs*（for FDEIA）, angiotensin converting enzymes (ACE) inhibitors（for angioedema）, etc
6) Autoantibodies against IgE or the high affinity IgE receptors
7) Underlying disease

Collagen and related disease（SLE, Sjögren's syndrome, etc), lympho-proliferating diseases, hereditary disorders (e.g. C1-INH deficiency）, serum sickness, other organ dysfunctions, circadian rhythm（idiopathic urticaria tends to aggravate from evening toward morning)

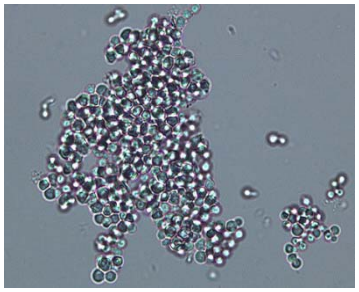
*: May act as either direct triggers or background factors.

Adapted from Guidelines for Management of Urticaria. Jap J Dermatol 121: 1339-1388, 2011 (in Japanese), & Allergol Int 61: 517-527, 2012 (in English)

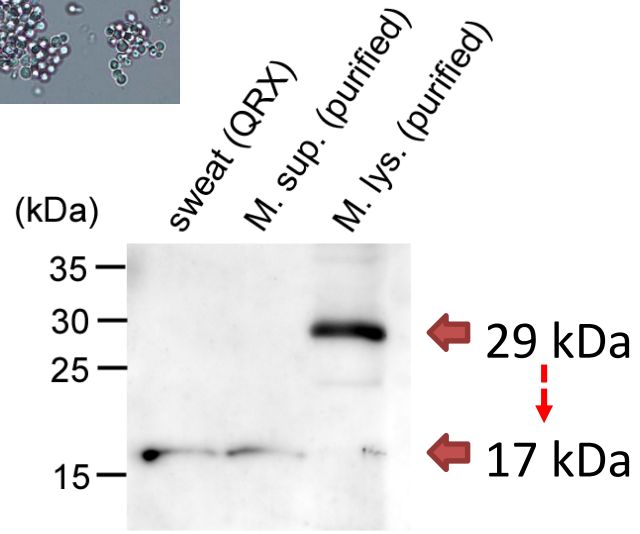
A histamine releasing antigen in sweat for basophils and skin test of patients with cholinergic urticaria has been identified as MGL_1304 released from *M.globosa* on the skin



	Cholinergic urticaria (n=35)	Control (n=14)
Positive (Histamine release >5%)	23/35 (66%)	0/14 (0%)



Malassezia globosa in culture



Smith-2 monoclonal antibody

MGL_1304 is synthesized as 29kDa protein, processed and released as a 17kDa protein .

Takahagi S, et al. Br J Dermatol 160: 426-428, 2009

Hiragun T, et al. J Allergy Clin Immunol 132:608-615.e604, 2013

Factors and possible underlying causes of CSU

controversial

Food: allergens, and psuedallergens (spices, salicyclic acid and other additives)

NSAIDs

ACI inhibitor*

(for Angioedema)

Fatigue
Stress
} (controversial)

Infections

Autoimmunity: against IgE*/FcεRIα*, thyroid tissues

*: May explain mast cell activation and/or vascular reactions

Clinical features of patients with chronic urticaria with or without autoantibodies

Evidences of ASST for association with clinical features

- *Sabroe RA, et al. J Allergy Clin Immunol 110: 492-499, 2002*
- *Toubi E, et al. Allergy 59: 869-873, 2004*
- *Caproni M, et al. Acta Derm Venereol 84: 288-290, 2004*
- *Staubach P, et al. Dermatol 212: 150-159, 2006*
- *Kulthanan K, et al. J Dermatol 34: 294-301, 2007*
- *Metz M, et al. J Allergy Clin Immunol 123: 705-706, 2009*
- *Alyasin S, et al. Allergy Asthma Clin Immunol 14;7 Suppl 2:A10, 2011*
- *Zhong H, et al. Allergy 69: 359-364, 2014*

Evidences of ASST against association with clinical features

- *Nettis, E, at al. Clin Exp Dermatol 27: 29-31, 2002*
- *Sahiner UM, et al. Int Arch Allergy Immunol 156: 224-230, 2011*

Causes and exacerbating factors of CSU

A variety of factors may be associated with exacerbation and improvement of the symptoms of CSU to various degrees. However, none of them explains the whole pathogenesis of CSU in most patients.

The pathogenesis urticaria has been studied in view points of

- Mechanism of mast cell activation
  - IgE mediated:
    - exogenous/endogenous antigen, anti-IgE, anti-FcεRIα
  - Serum factors:
    - Complements, histamine release factors (identified and unidentified)
  - Neuropeptides, proteases, etc
- Mediators released from mast cell
  - histamine, prostaglandins, PAF, bradykinin, cytokines, etc
- Histopathology
  - Mast cells, lymphocytes, eosinophils, neutrophils, basophils
- Trigger/underlying causes
  - Exogenous antigens
  - Physical stimuli
  - Infections *H. Pylori* infection)
  - Diet (pseudoantigens, etc)
  - Biomarkers
- Treatments
  - Targeting histamine, inflammation/immune system, IgE, coagulation system, etc.

= translationally controlled tumor protein (Kawakami, 2014)

antihistamines

Omalizumab

EAACI global guideline (2014)

Allergy 2014; 69: 868-887

First line:

Modern second generation antihistamines

↓ *if symptoms persist after 2 weeks*

Second line:

Increase dosage up to fourfold of modern second generation antihistamines

↓ *if symptoms persist after 1-4 further weeks*

Third Line:

Add on to second line*: Omalizumab or Ciclosporin A or Montelukast

Short course (max 10 days) of corticosteroids may also be used at all times if exacerbations demand this

*the order of third line treatments does not reflect preference.

Algorithm in the practice parameters of urticaria published by AAAAI, ACAAI and JCAAI (2014)

Bernstein J, et al. J Allergy Clin Immunol 2014; 133: 1270-7

STEP 4

Add an alternative agent

- Omalizumab or cyclosporine
- Other anti-inflammatory agents, immunosuppressants, or biologics

STEP 3

Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

STEP 2

One or more of the following:

- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H_2- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine to be taken at bedtime

STEP 1

- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

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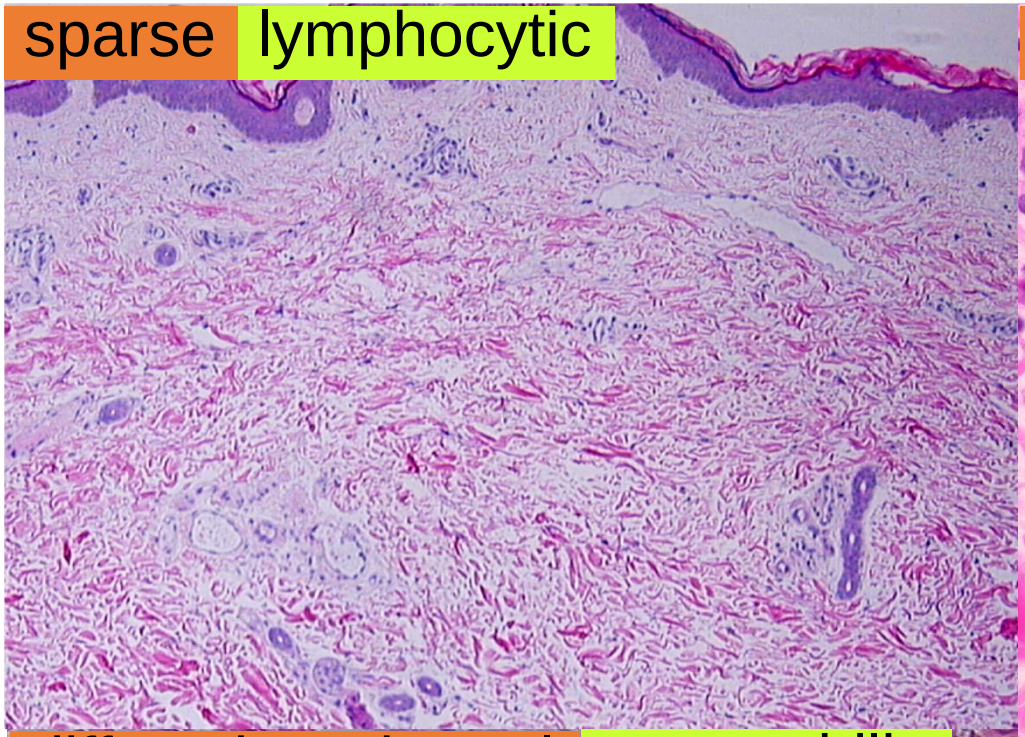
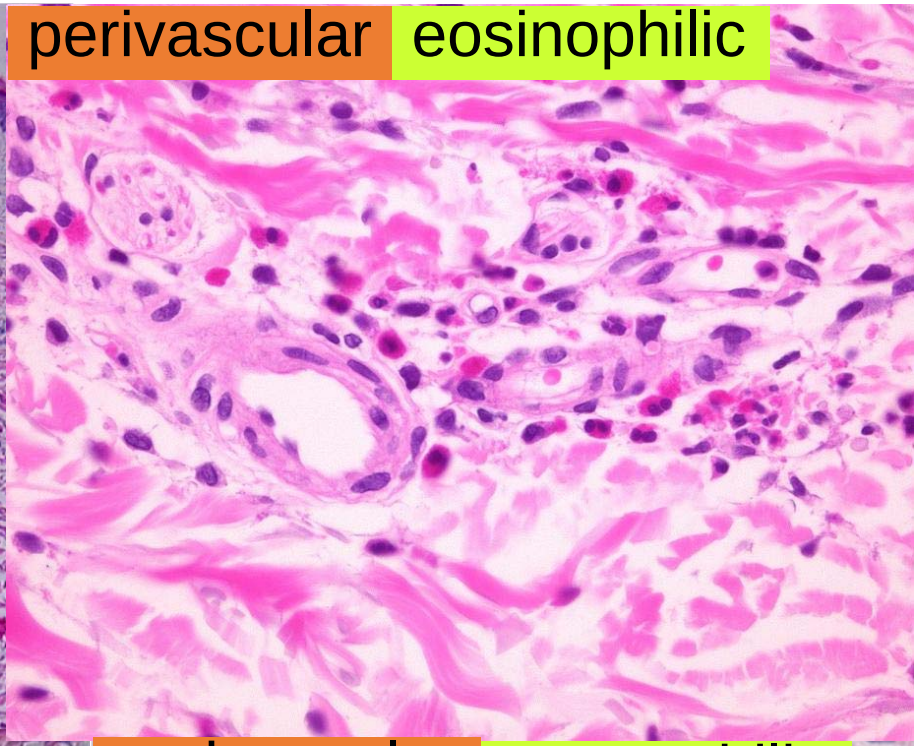
  - Exogenous antigens
  - Physical stimuli
  - Infections (*H. Pylori* infection, virus, etc)
  - Diet (pseudoantigens, etc)
  - Biomarkers
- Targets of treatments
  - Targeting histamine, inflammation/immune system, IgE, coagulation system, etc.

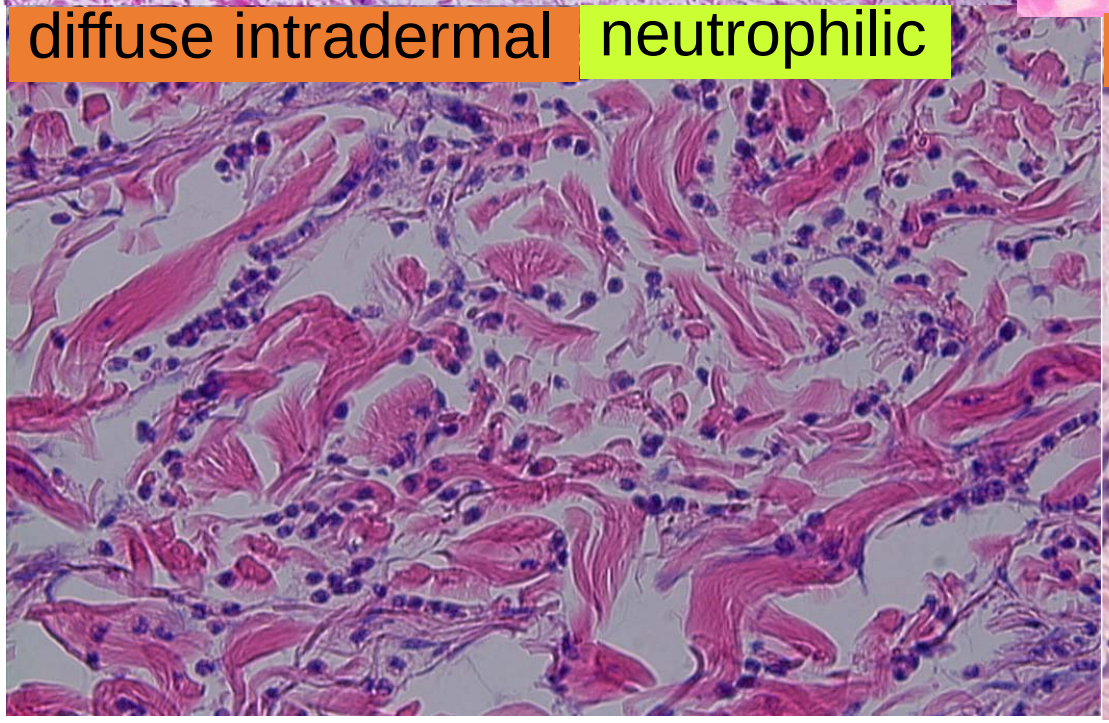
= translationally controlled tumor protein (Kawakami, 2014)

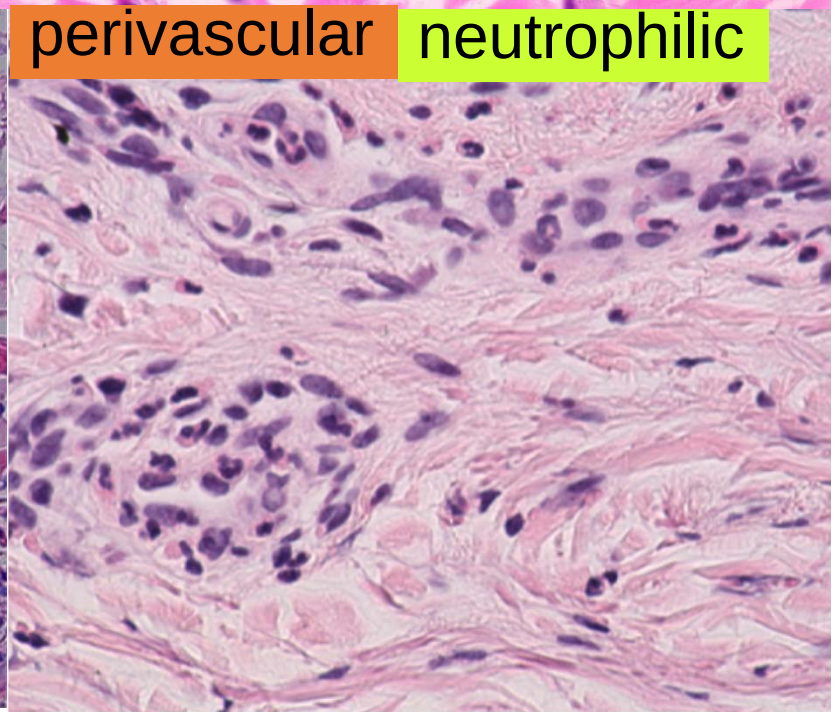
antihistamines

Omalizumab


sparse lymphocytic

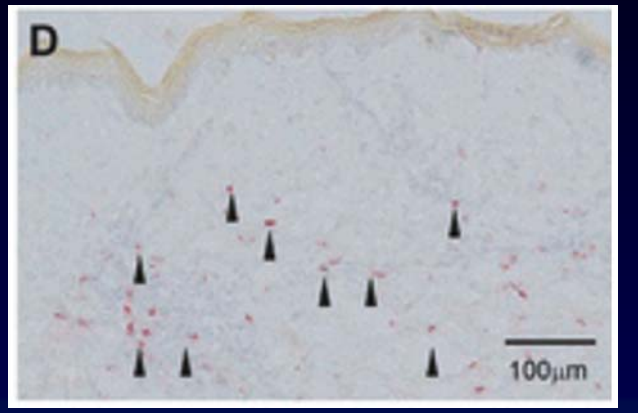

perivascular eosinophilic


diffuse intradermal neutrophilic


perivascular neutrophilic

Involvement of basophils in CSU

- Basophils are observed in skin lesion of CSU.
- Number of peripheral blood basophils are decreased (Basopenia) in patients with CSU in correlation to the severity of CSU.

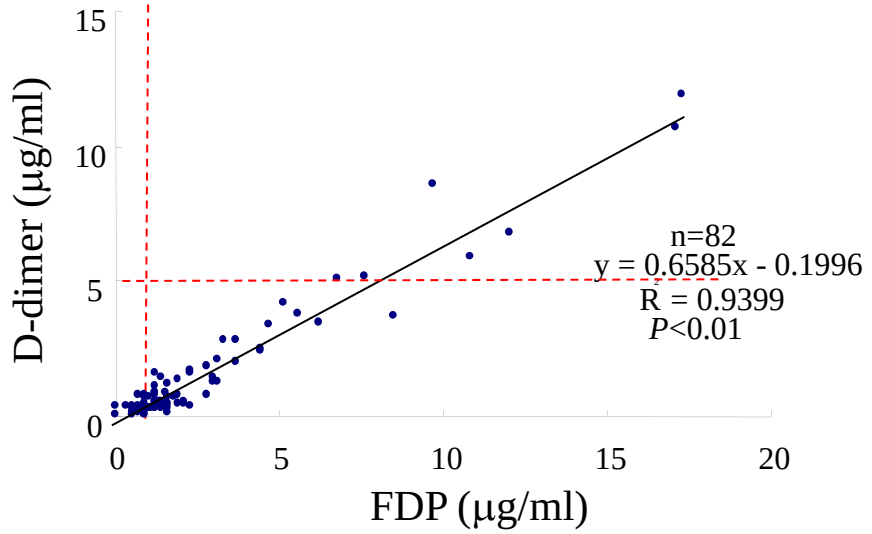


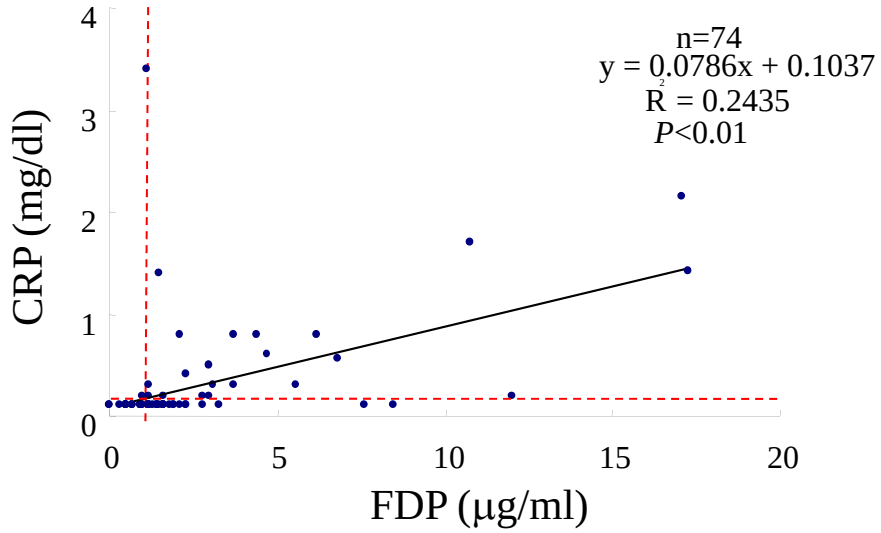
- Basophils of many patients with CSU are low- or non-responsive to anti-IgE antibody.
- Both decreases in number and in response to anti-IgE antibody of basophils recover either by natural course or the treatments of CSU.

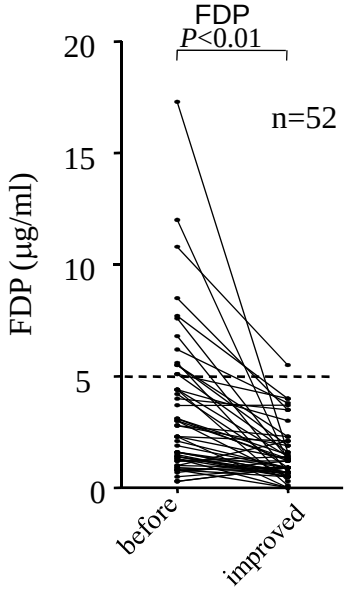
Ito Y, et al. Allergy 66: 1107-1113, 2011.

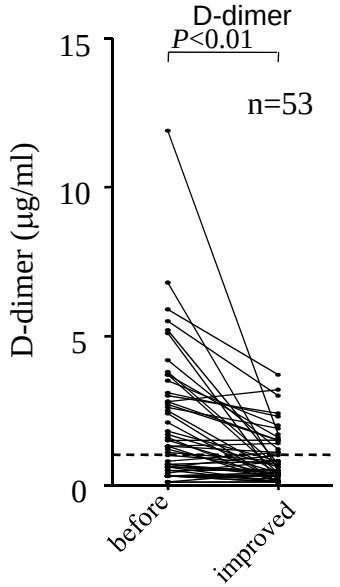
Borriello F, et al. Basophils and Skin Disorders. J Invest Dermatol 134:1202-10, 2014.

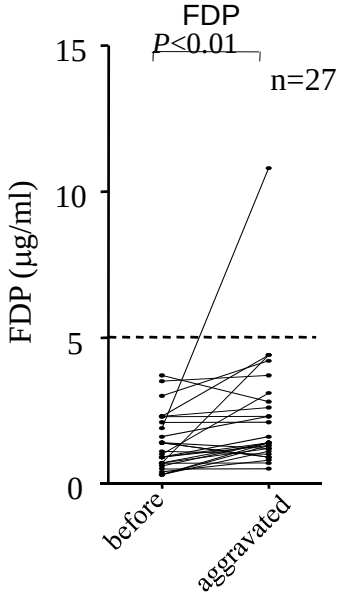
Levels of plasma FDP, D-dimer and serum CRP are both elevated in correlation to disease activities

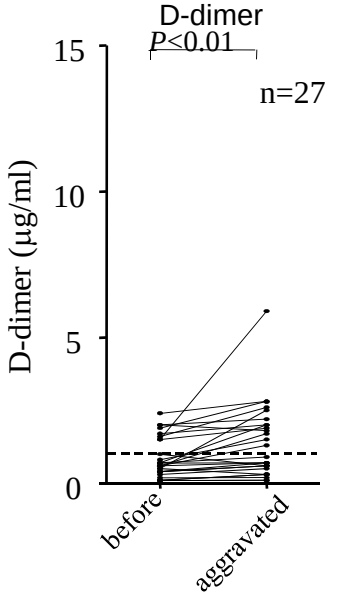










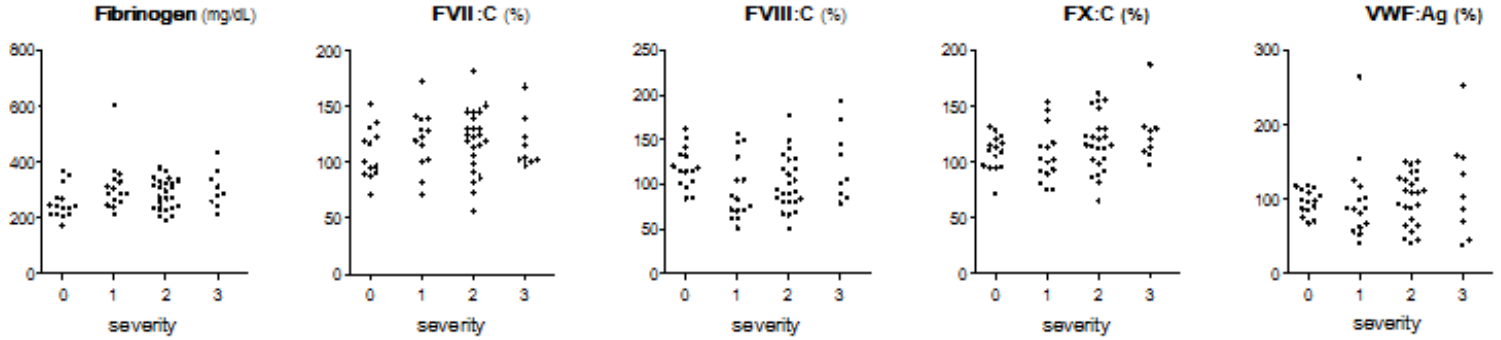


Takahagi S, et al. Allergy 65: 649-656, 2010

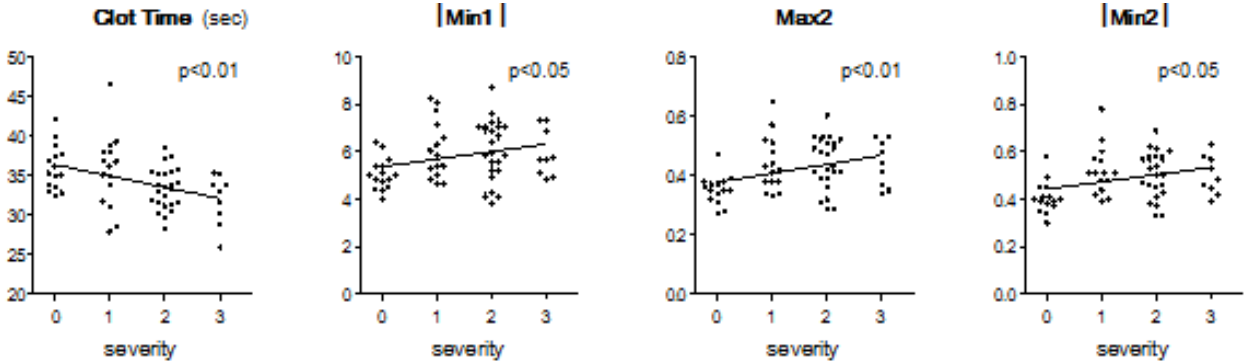
Blood coagulation potential is increased in CSU

Takeda, et al. Allergy, 66: 428, 2011

Coagulation factor cconcentration



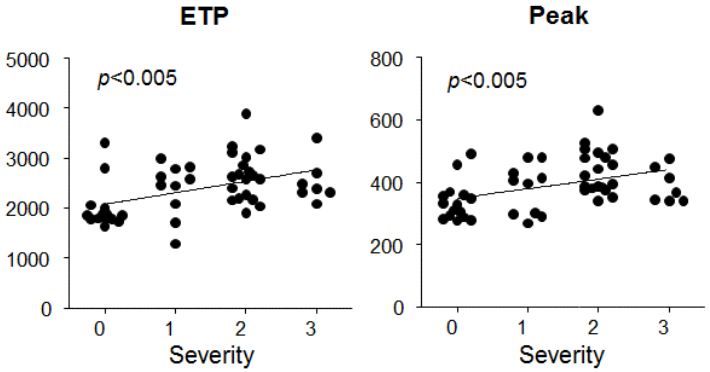
APTT clot waveform analysis (represents coagulation potential *in vitro*)

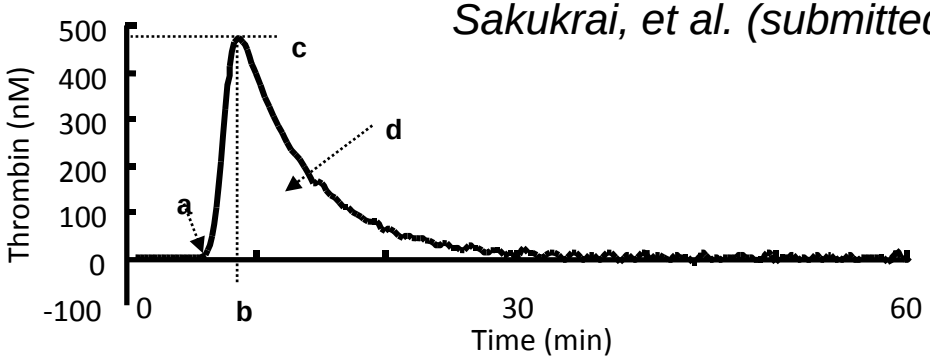


Takeda, et al. Allergy, 66: 428, 2011

Calibrated automated thrombography (CAT) (Thrombin produce potential *in vitro*)

Sakukrai, et al. (submitted)

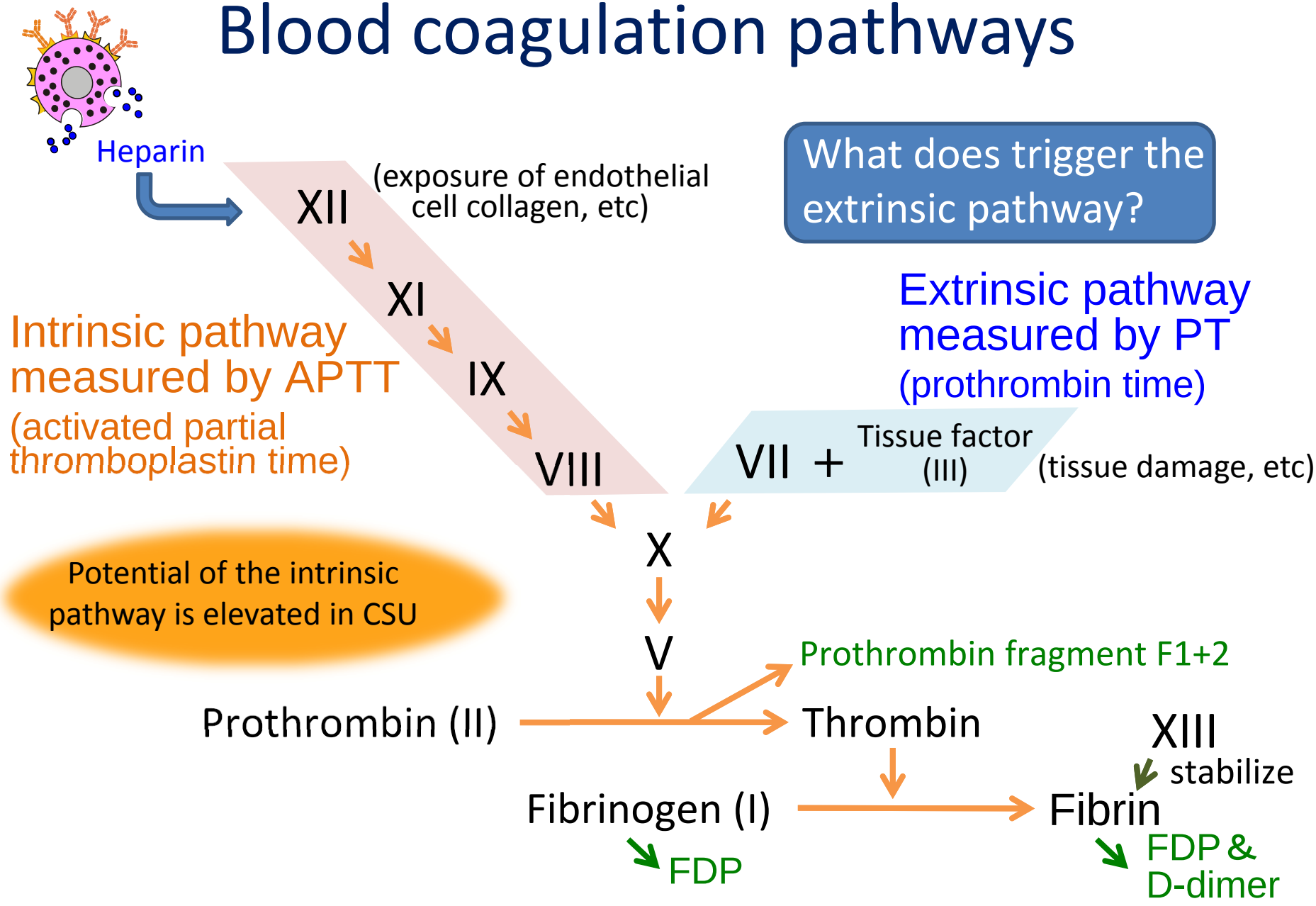




Cases treated by medications with anti-coagulation/fibrinolysis activities

Authors and subjects	Preceding treatments	Medications	Results
Chua SL, Gibbs S (2005), 1 case	Resistant for anti-histamines and immune-suppressants	Heparin subcutaneous injections（5000 units × 2/day）	A case report. Remission, and recurrent on stop medication.
Asero et al. (2010), 8 cases	Resistant to anti-histamines and steroids. Increase of coagulation markers.	Heparin subcutaneous injections（11,400 units/day）＋tranexamic acid 1g × 3/day (oral)	Very effective for 5 out of 8 cases
Parslew et al. (2000), 8 cases	Resistant for anti-histamines	Warfarin（PT-INR: 2-2.5）	Effective for 6 out of 8 cases
Mahesh et al. (2009), 5 cases	Resistant for anti-histamines and steroids. APST positive	Warfarin（PT-INR: 1.1-1.8）	Effective for 4 out of 5 cases
Takahagi et al. (2010) , 2 cases	Resistant for anti-histamines and immune-suppressants.	Protease inhibitor (Nafamostat mesilate; NM, div, and camostat mesilate; CM, oral).	Eruptions disappeared during NM div, and recurred when stopped div. Symptoms of one case were effectively suppressed by oral CM.

Blood coagulation pathways

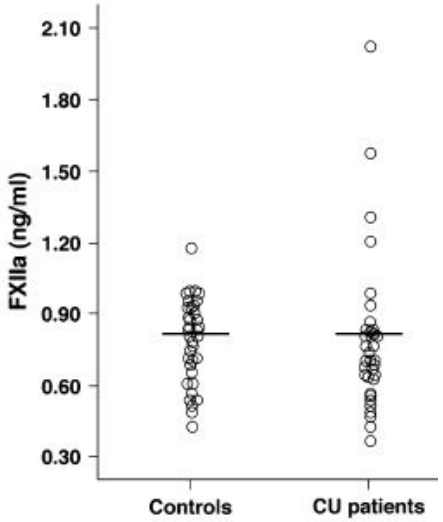


- The coagulation process is initiated by the extrinsic pathway with an exposure to tissue factor, followed and enhanced by the activation of the intrinsic pathway and results in fibrin formation.

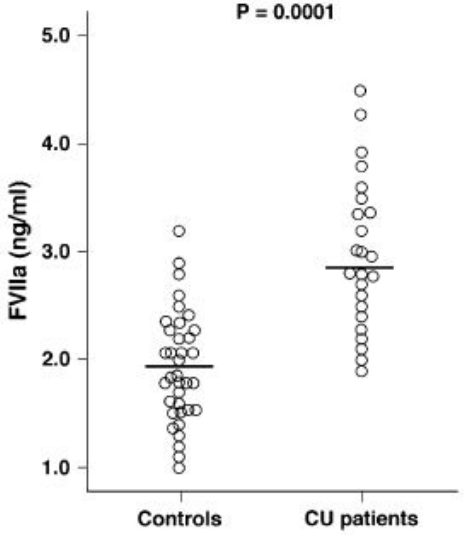
What is the mechanism of coagulation/fibrinolysis in chronic urticaria?

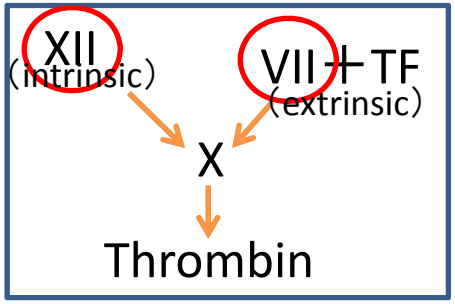
*Asero et al. JACI **119**: 705-710, 2007*

Activated Factor XII

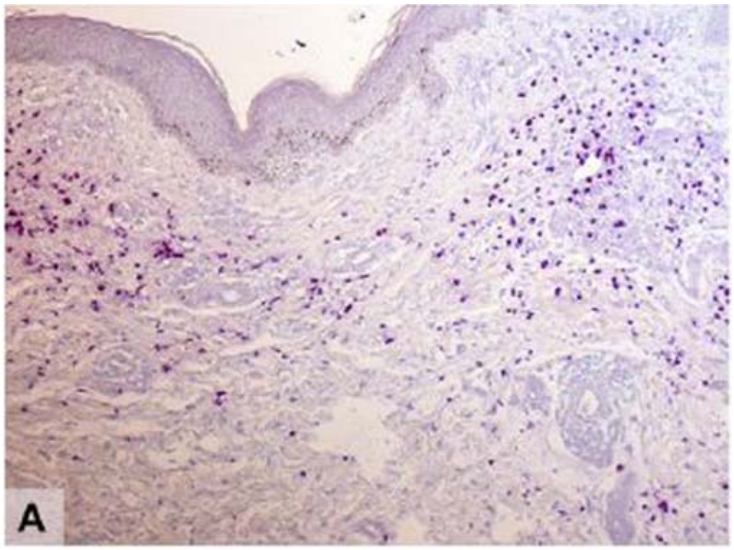


Activated FVII



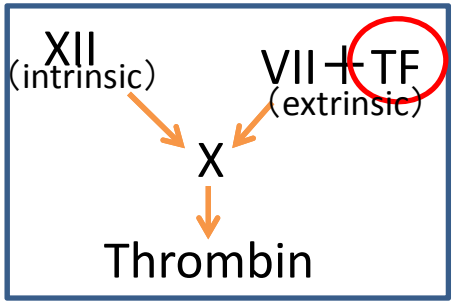


- Asero, et al reported the increase of FVIIa (initiator of the extrinsic pathway), but not FXIIa (initiator of the intrinsic pathway) in CSU.

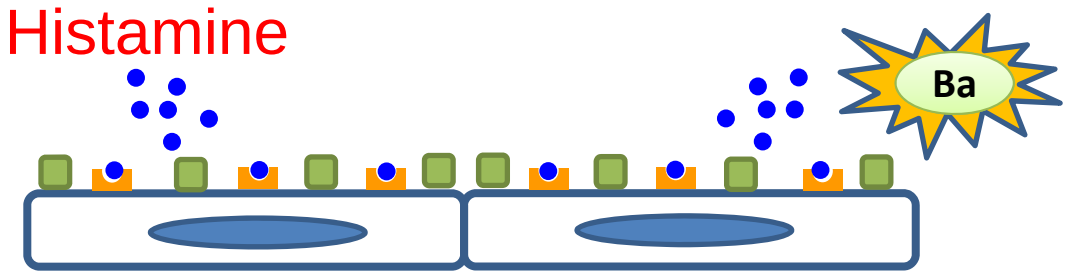


*Cungo et al. IAAI **148**: 170-174, 2008*

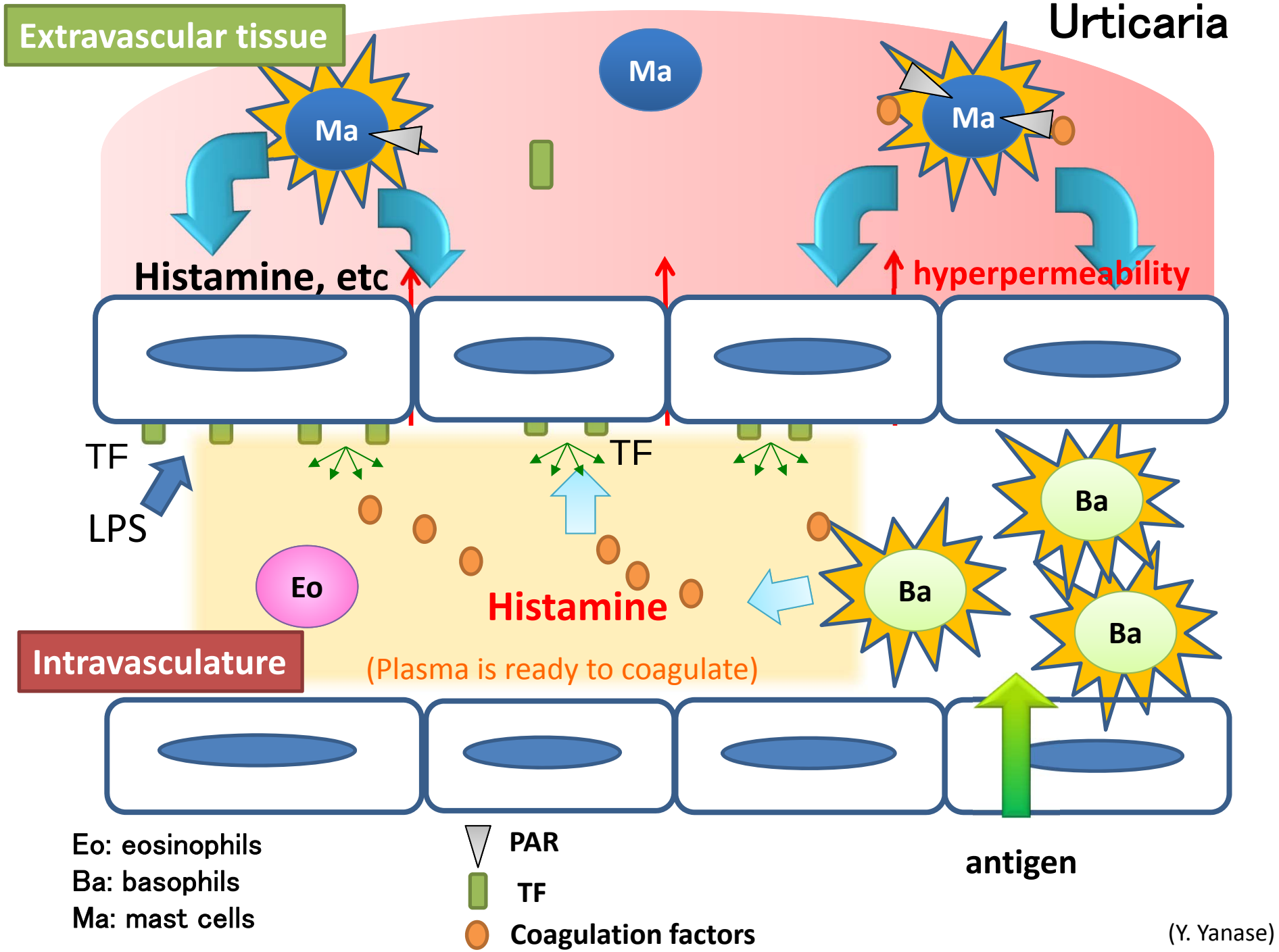
- They also revealed the expression of TF in eosinophiles in the site of wheal formation.



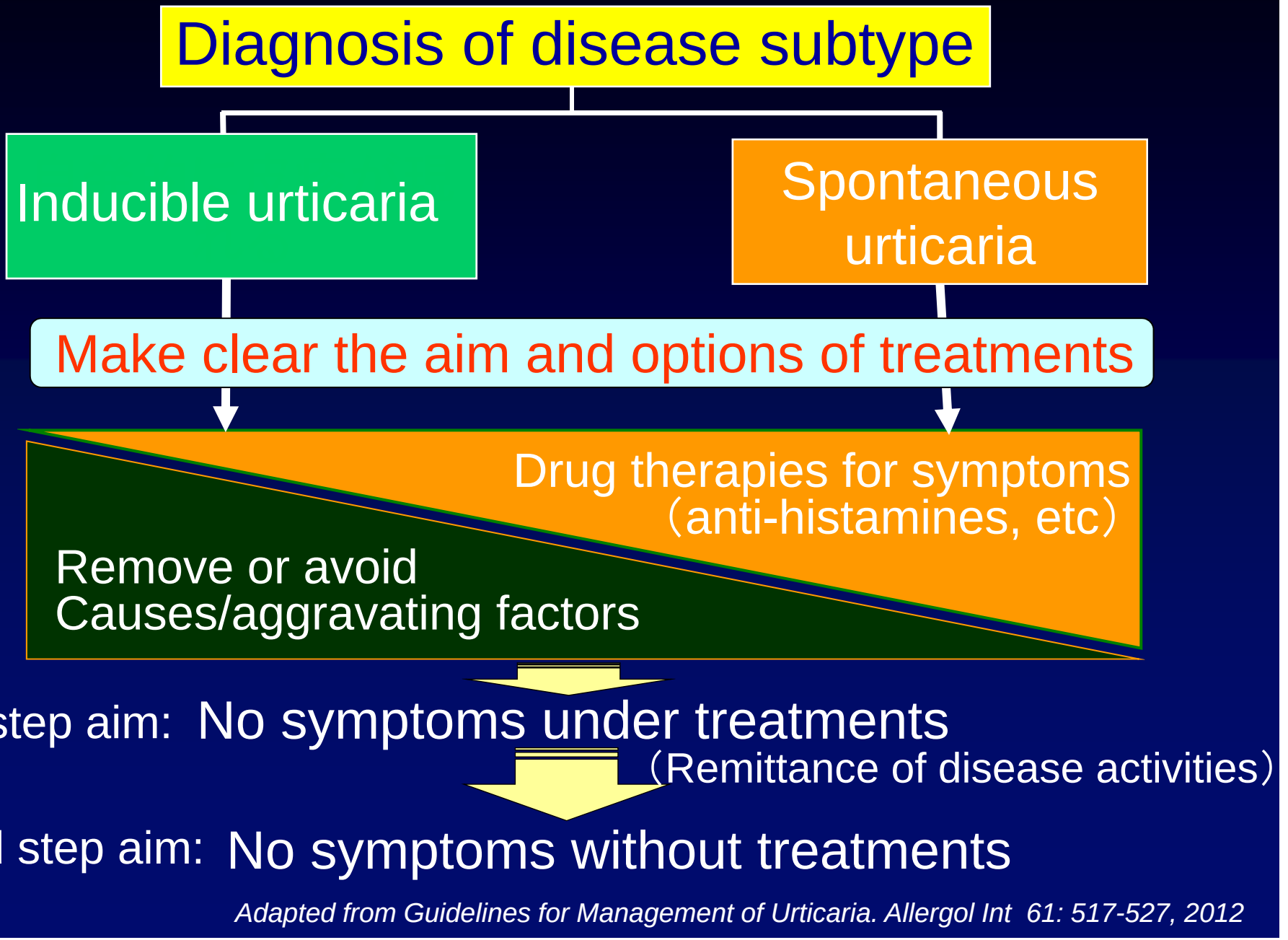
TF expression by endothelia cells is induced by histamine and basophils via H1-receptor



(Y. Yanase, et al. unpublished data)


Urticaria
Extravascular tissue
Ma
Ma
Ma
Histamine, etc
hyperpermeability
TF
TF
LPS
Eo
Histamine
(Plasma is ready to coagulate)
Intravasculature
Ba
Ba
Ba
Eo: eosinophils
Ba: basophils
Ma: mast cells
PAR
TF
Coagulation factors
antigen
(Y. Yanase)

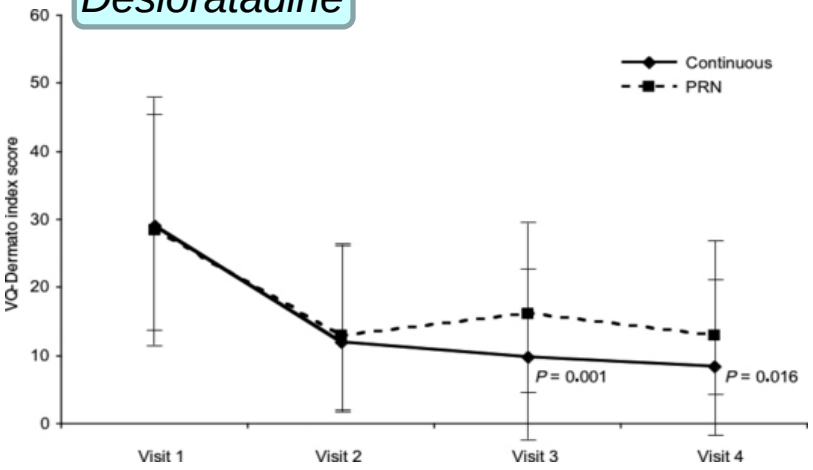
Principle of the management of urticaria



Adapted from Guidelines for Management of Urticaria. Allergol Int 61: 517-527, 2012

Continuous vs on demand use of antihistamine

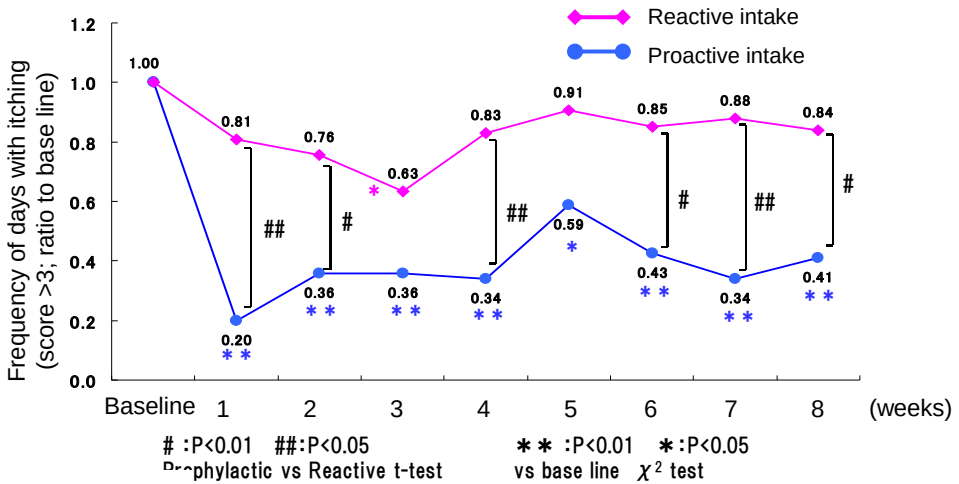
Desloratadine



Grob JJ, et al. Allergy 64: 604-612, 2009

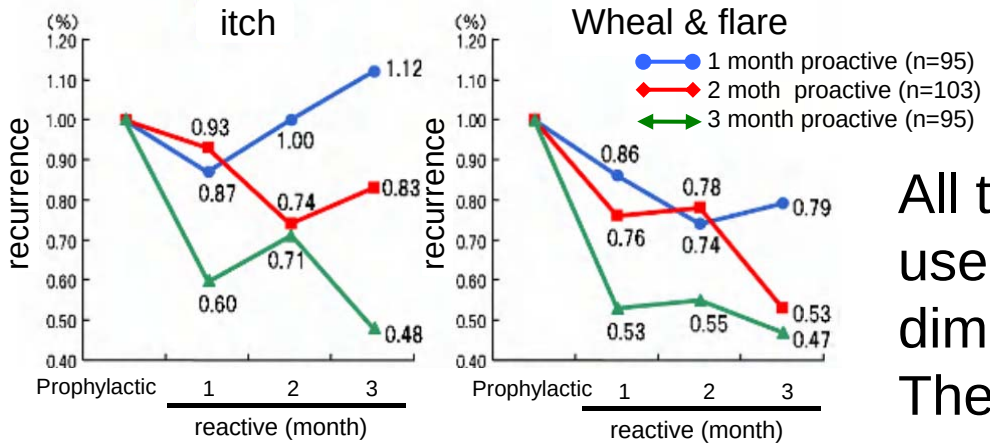
Epinastine

Time course of itching in day time: Number of days when itch score was >3



Furukawa F, et al. Rinsho Hifuka 63: 691-699, 2009

Ebastine

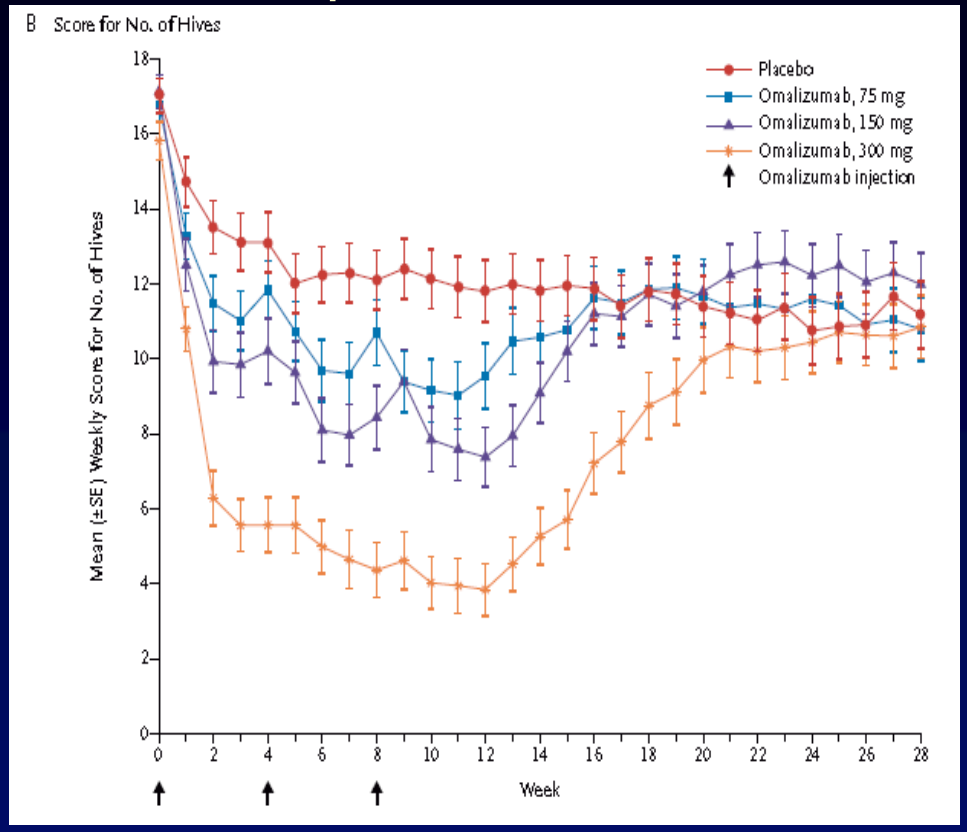


Kawashima M, et al. Risho Hifuka 64: 523-531, 2010

All three studies endorse proactive use of antihistamine after the diminishment of symptoms.
The effect of them on "cure“ remains as uncertain.

Long term effect of omalizumab on chronic urticaria

Chronic spontaneous urticaria



Maurer M, et al. N Engl J Med. 2013;368: 924-935

Solar urticaria

Cold urticaria

Heat urticaria

Cholinergic urticaria

Delayed pressure urticaria

Mechanical urticaria

Urticarial vasculitis

⋮

Metz M, et al. 2014 JAMA D, 2014 JDS
Kai A, et al. 2014 CED
Kaplan A 2012 AAIR
etc, etc.

Omalizumab has been reported to be effective for subtypes of chronic urticaria, regardless of the autoimmunity, suggesting the important role of IgE in the common mechanism of urticaria.

It does not appear to bring "cure" of urticaria.

Effect of 1 month proactive treatment with oral anti-histamine on recurrence over 3 month

Even if no Sx for 1 month, 40% recurred in a month after stopping anti-histamine

1 month proactive treatment reduced the recurrence in 3 months

(Hide, unpublished data)

Thank you for your attention