6 December 2012:
13:30-15:00 G.04 (HICC)

The Hyderabad International Convention Centre (HICC) in Hyderabad, India

WISC 2012; WAO International Scientific Conference

Postgraduate Course 16: URTICARIA & ANGIOEDEMA TRACK
-Understanding and Managing Acute and Chronic Urticaria

Approach to Refractory Urticaria and Angioedema

Chairpersons: Korad Bork (Germany),
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Frequently raised complaints by patients with urticaria and angioedema

1.Intolerable symptoms in spite of treatments

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

(Definition of health in the WHO constitution)

Frequently raised complains by patients with urticaria and angioedema

1.Intolerable symptoms in spite of treatments

Health status scores in patients with CSU are comparable to those in patients with coronary artery disease

2.What is the cause of my urticaria?

Food?, Sick of internal organs?, etc.

3.How long does it take for cure?

Please treat at causative level, not symptomatically
Do I suffer from urticaria for life long?

4.I don't like drugs just for symptoms

I don't want to be dependent on drugs.

Principle of the management of urticaria

In general,

- Urticaria inducible by certain stimuli are resistant for medications.

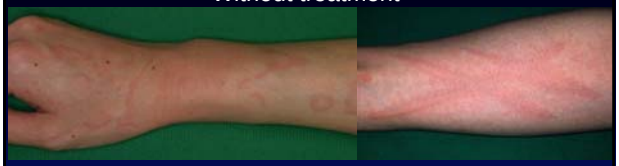
whereas

- Urticaria characterized by spontaneously appearing wheals are subject to medications, especially antihistamines.

Chronic spontaneous urticaria

Mechanical urticaria

Without treatment



Under treatment

Symptoms of CSU may be completely suppressed, but those of mechanical urticaria are partially suppressed only.

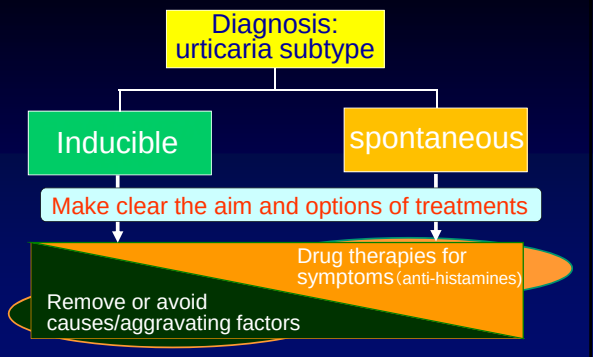
The efficacy of systemic steroid on urticaria depends of subtypes urticaria

Subtypes of urticaria	Expectable	Not expectable
Spontaneous urticaria	Acute and chronic spontaneous urticaria (including autoimmune urticaria)	–
Inducible type urticarias	Delayed pressure urticaria (DPU)	Urticarias due to type I allergy and NSAIDs intolerance, the other physical urticarias, etc.
Angioedema	Spontaneous/idiopathic urticaria (histaminergic)	Other types of angioedema, HAE・ACEI induced angioedema, etc.
Diseases related to urticaria	Urticarial vasculitis	Urticaria pigmentosa, Schnitzler syndrome, CAPS

Principle of the management of urticaria

It is important to distinct acute and chronic spontaneous urticaria (CSU) from the other types of urticaria, not only because the absence of direct trigger for exciting wheal formation, but also because responsiveness to treatments, especially steroids.

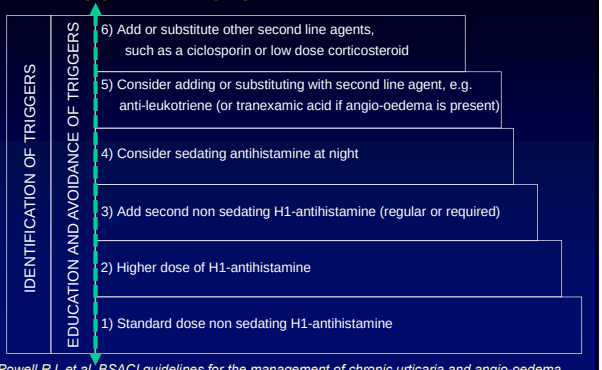
Principle of the management of urticaria



Adopted from Guidelines for Management of Urticaria. Jap J Dermatol 121: 1339-1388, 2011 (in Japanese), & Allergol Int 2012 [Epub ahead of print]

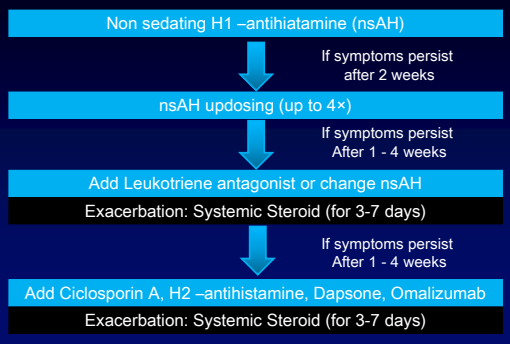
Management of chronic spontaneous urticaria (CSU)

Algorithm for the treatment of CSU suggested by guidelines: *BSACI, 2007*



Powell RJ, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy 2007; 37:631-650

Algorithm for the treatment of CSU suggested by guidelines: *EAACI, 2009*



Zuberbier T, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. Allergy 2009; 64:1427-1443

Algorithm for the treatment of CSU suggested by guidelines: *JDS, 2011*

①Anti-histamines

①standard doses, ②change drugs, ③increase doses

②Supplementary medications

e.g. H_2-blockers*, anti-leukotrienes*, extracts of inflammatory rabbit skin inoculated with vaccinia virus, glycyrrhizinic acid, dapsone, anti-anxiety drugs, tranexamic acid

*Off label use

③Steroids

corticosteroids, equivalent to 5-15 mg/day prednisolone

④Experimental trials

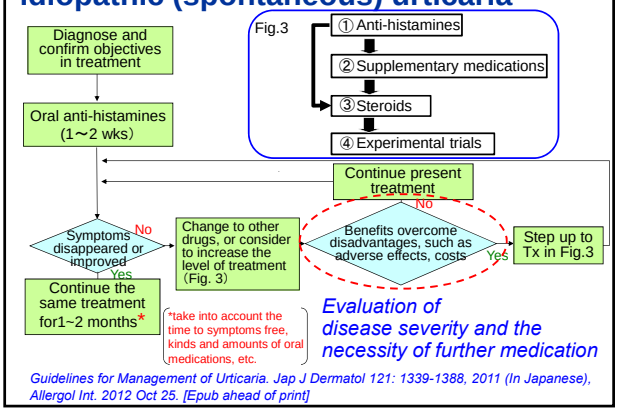
immunological treatments (e.g. CisA*, corticosteroids, equivalent >20 mg/day)

Hide M, et al. Guidelines for Management of Urticaria. Jap J Dermatol 121: 1339-1388, 2011 (in Japanese), & Allergol Int 2012 [DOI: 10.2332/allergolint.12-RAI-0497]

Stages of the refractory urticaria and angioedema

1. Intolerable symptoms in spite of vigorous treatments
2. No or mild symptoms on heavy load of treatments (adverse effects, cost, cumbersomeness)
3. No or mild symptoms on treatments with mild or moderately heavy load of treatments
4. No or mild symptoms on safe and readily available treatments, such as antihistamines, but recur if stop medication

Algorism for treatment of chronic idiopathic (spontaneous) urticaria



Guidelines for Management of Urticaria. Jap J Dermatol 121: 1339-1388, 2011 (In Japanese), Allergol Int. 2012 Oct 25. [Epub ahead of print]

Three points to be taken for the management of refractory urticaria and angioedema

1. How to suppress apparent symptoms?
2. How to control underlying disease activities towards remission/cure?
3. Balance for the effect and burdens
4. Time course towards the remission/cure

Treatments for CSU that is not sufficiently controlled by level 1 treatment (nsAH, 1x): *EAACI guideline, 2009*

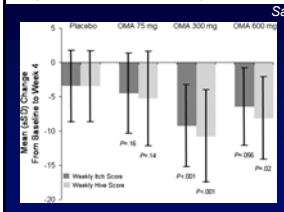
Level	Medication	Cost	Safety profile	Evidence for efficacy
2nd	nsAH updosing (up to 4x)	Low	Good	Good
3rd	add LT antagonist or change nsAH	Low-to medium-low	Good	Insufficient or no evidence in high quality RCT
4th	CisA	Medium to high	Moderate	Very low level
	H2-antihistamine	Low	Good	Very low level
	Dapsone	Low	Medium level of side effects	Low level
	Omalizumab	High	Good	High level

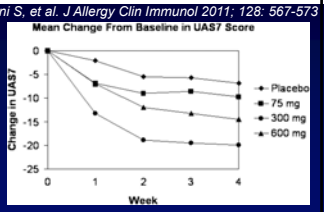
Atopic dermatitis and skin disease

A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H_1-antihistamine–refractory chronic idiopathic urticaria

Sarbjit Saini, MD,[a] Karin E. Rosen, MD, PhD,[b] Hsin-Ju Hsieh, PhD,[b] Dennis A. Wong, MD,[b] Edward Conner, MD,[b] Allen Kaplan, MD,[c] Sheldon Spector, MD,[d] and Marcus Maurer, MD[e] *Baltimore, Md, South San Francisco and Los Angeles, Calif, Charleston, SC, and Berlin, Germany*

Saini S, et al. J Allergy Clin Immunol 2011; 128: 567-573





Increasing number of reports about the efficacy of omalizumab has been published. It is beyond both serum IgE concentrations and urticaria subtypes

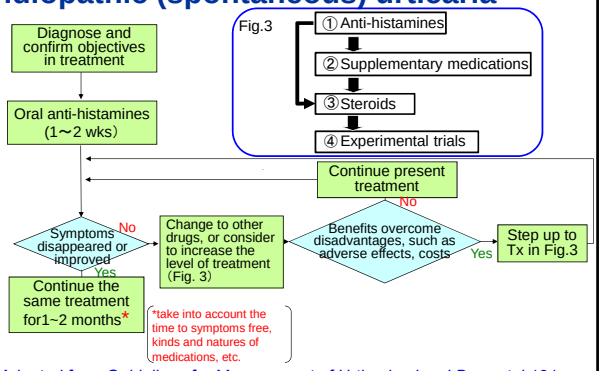
Immunosuppuressive/modulative treatments for urticaria

	Chronic	Other type
Steroid（PDN>20mg/d）	○**	Anaphylaxis
Plasmapheresis	○*	–
CisA	○** (RCT)	solar
Methotrexate	○ *	–
Cyclophosphamide	○ *	–
IVIG	○*	–
Mycophenolate	○*	–
Hydroxychloroquine	○**	–
Omalizumab	○** (RCT)	cholinergic, cold, etc

* For autoimmune urticaria * For non autoimmune urticaria

∗ The effectiveness is for reducing/suppressing symptoms, not necessarily for cure. They may also applied for non-autoimmune urticaria

Algorism for treatment of chronic idiopathic (spontaneous) urticaria



Adapted from Guidelines for Management of Urticaria. Jap J Dermatol 121: 1339-1388, 2011 (In Japanese), Allergol Int. 2012 Oct 25. [Epub ahead of print]

CQ12：Should idiopathic urticaria continued to be treated for a certain period after a disappearance of symptoms?

Comments：Idiopathic urticaria should continued to be treated for a while after disappearance or decrease of the symptoms.

Recommendation level：B, Evidence level II

References：
1) Grob JJ, et al: How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life, *Allergy*, 2009; 64: 605-612.
2) Furukawa F, et al：The comparison of proactive and reactive treatments on chronic urticaria. (in Japanese), *Rinshou Hifuka, 2009; 63：691−699.*
3) Kawashima M, Kohno T：The effect of different durations of proactive treatment with anti-histamine on the prognosis of chronic urticaria. (in Japanese), *Rinshou Hifuka, 2010; 64: 523-531.*

Guidelines for Management of Urticaria. Jap J Dermatol 121: 1339-1388, 2011 (In Japanese), Allergol Int. 2012 Oct 25. [Epub ahead of print]

Management of inducible type urticaria

Inducible type urticarias are mostly refractory to antihistamines

Physical urticaria
- Mechanical urticaria (Symptomatic Dermographism)
- Cold urticaria
- Solar urticaria**
- Heat urticaria
- Delayed pressure urticaria (DPU)

Other urticaria types
- Cholinergic urticaria**
- Aquagenic urticaria
- Contact urticaria*
- Allergic urticaria*

Angioedema (except for bradykinin mediated angioedema)

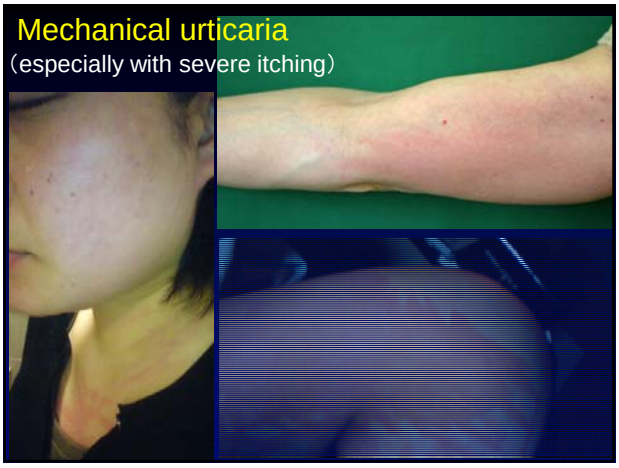
*Avoidance of exciting factor
**Hardening/tolerance induction

Reported treatments for inducible type urticarias

	Avoid triggers	Hardening /tolerance	Steroids	Omalizumab
Mechanical urticaria	✓			✓✓
Cold urticaria	✓	✓		✓✓
Solar urticaria	✓✓	✓✓		✓✓
Heat urticaria	✓✓			✓✓
Aquagenic urticaria	✓			
DPU	✓		✓✓	
Cholinergic urticaria	✓	✓~✓✓		✓✓
Contact urticaria	✓✓	✓✓		
Allergic urticaria	✓✓✓			✓
Angioedema	✓✓			✓✓

Mechanical urticaria

(especially with severe itching)



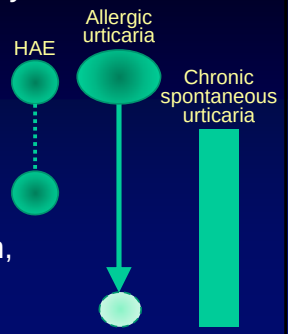
Effects of Ciclosporin on refractory mechanical urticaria

No	Age /Sex	Duration (yr)	CsA dose (mg/kg/day)	Duration of CsA (month)	Previous medications	Outcome	Adverse effects
1	56/M	4	3.0	21	H_1-antagonists in 3-fold doses, corticosteroids (5mg/day, 2 weeks)	Cure	None
2	67/F	5	3.4	16, continue	H_1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (2.5-20mg/day, 2 years)	Improvement	None
3	25/F	12	2.5	32, continue	H_1-antagonists in 3-fold doses, H_2-antagonists, leukotriene antagonists, corticosteroids (2.5-7.5mg/day, 2 years)	Improvement	Epigastric distress
4	26/F	0.5	2.7	8, continue	H_1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (10-30mg/day, 2 weeks)	Improvement	None
5	65/F	15	2.0	0.5	H_1-antagonists in 4-fold doses, corticosteroids (5mg/day, 2 weeks)	Inefficiency	None
6	43/M	5	0.8	0.25	H_1-antagonists in 3-fold doses, leukotriene antagonists	Inefficiency	Headache, nausea

Toda S, et al. Allergol Int 2011; 60: 547-550

Taxonomy of the treatment for urticaria and view points for practice

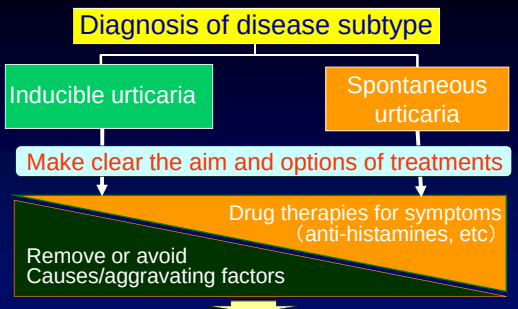
- Short time, temporary actions
  - Adrenalin injection
  - Antihistamine (iv, im, po),
  - Steroid infusion
  - Plasmapheresis, IVIG, etc
- Long time control
  - Antihistamine
  - Auxiliary medications
  - Oral steroids, etc
- Long time remission, cure
  - Desensitization
  - Prophylactic use of antihistamines, etc



Taxonomy of the treatment for urticaria and view points for practice

- Short time, temporary actions
  - Adrenalin injection
  - Antihistamine (iv, im, po),
  - Steroid infusion
  - Plasmapheresis, IVIG, etc
  - Effects on symptoms
- Long time control
  - Antihistamine
  - Auxiliary medications
  - Oral steroids, etc
  - Effects on symptoms
  - Burden for patients (safety, cost, convenience, etc.)
- Long time remission, cure
  - Desensitization
  - Prophylactic use of antihistamines, etc
  - Effects on disease itself

Principle of the management of urticaria



No symptoms under treatments

(Remittance of disease activities)

No symptoms without treatments

Thank you for your listening

Night scene in Hiroshima