

두드러기 표준치료 항히스타민제 치료에 효과 있을 때와 없을 때

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Urticaria

Definition

Urticaria is a condition characterized by the development of wheals (hives), angioedema or both.

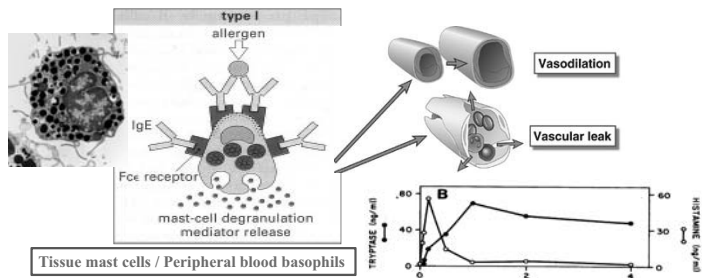
(A). wheal in patients with urticaria has 3 typical features:

1. a central swelling of variable size, almost invariably surrounded by reflex erythema,
2. an itching or sometimes burning sensation,
3. a fleeting nature, with the skin returning to its normal appearance, usually within 30 minutes to 24 hours.

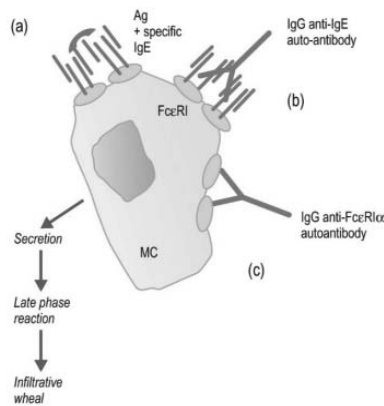
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3.3 | Pathophysiological aspects

Urticaria is a mast cell-driven disease. Histamine and other mediators, such as platelet-activating factor (PAF) and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilatation and plasma extravasation as well as cell recruitment to urticarial lesions. The mast cell-activating signals in urticaria are ill-defined and likely to be heterogeneous and diverse. Histologically,



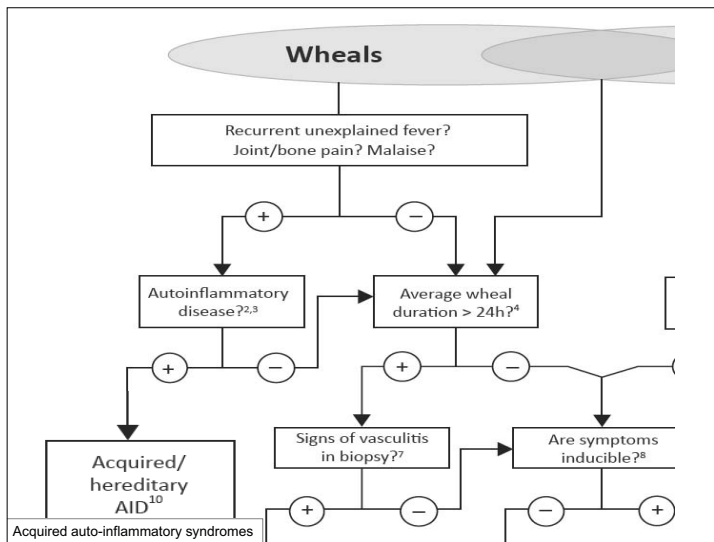
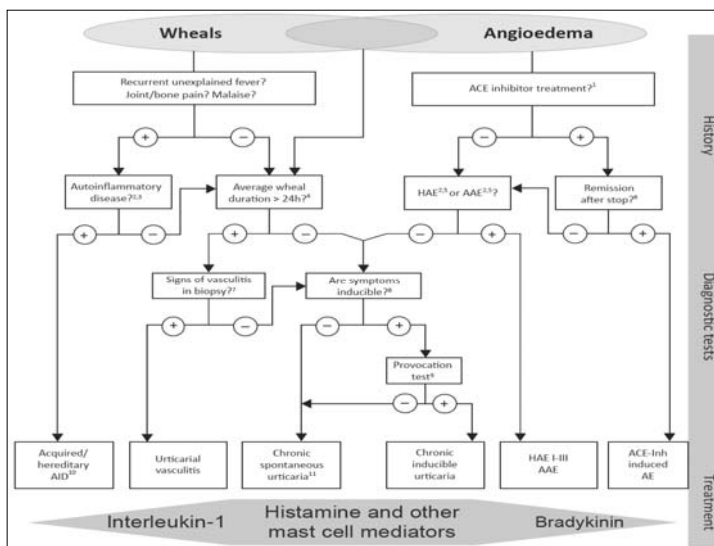
Mast cell-driven disease



- Autoimmune Theory
 - 30%- 40% of patients with CIU
 - Thyroid auto-Abs and thyroid dysfunction
- Non-immunological stimuli
 - Cytokines / neuropeptides
- Inducible stimuli
 - Cold, heat, sunlight, pressure

두드러기 진단

- **Urticaria** (hives) are transient lesions that are composed of a central wheal surrounded by an erythematous halo
 - Wheal and flare reaction
 - Itching or, sometimes, burning
 - Usually persist for < 24hrs



Diseases related to urticaria for historical reasons, and syndromes that present with hives and/or angioedema

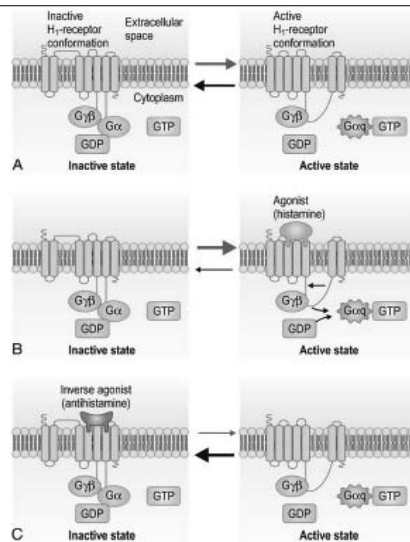
- Maculopapular cutaneous mastocytosis (urticaria pigmentosa)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (eg, HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches), that is familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) or neonatal-onset multisystem inflammatory disease (NOMID).
- Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
- Gleich's syndrome (episodic angioedema with eosinophilia)
- Well's syndrome (granulomatous dermatitis with eosinophilia/eosinophilic cellulitis)
- Bullous pemphigoid (prebullous stage)

항히스타민제 용법

The main option in therapies aimed at symptomatic relief is to reduce the effect of mast cell mediators such as histamine, PAF and others on the target organs. Many symptoms of urticaria are mediated primarily by the actions of histamine on H_1 -receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). Thus, continuous treatment with H_1 -antihistamines is of eminent importance in the treatment of urticaria (safety data are available for use of several years continuously). Continuous use of H_1 -antihistamines in CU is supported not only by the results of clinical trials^{97,98} but also by the mechanism of action of these medications, that is that they are inverse agonists with preferential affinity for the inactive state of the histamine H_1 -receptor and stabilize it in this conformation, shifting the equilibrium towards the inactive state.

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H1-ANTI-HISTAMINES



Inverse agonists

Treatments

1. Nonsedating, newer-generation antihistamines
(Fexofenadine, loratadine, desloratadine*, cetirizine, and levocetirizine*)
- Continuously and regularly
2. Elimination of aggravating stimuli (e.g., cold air)
3. Avoidance of aspirin and other NSAIDs (advisable)
- Exacerbations in 1/3 CU patients

• Study showed benefit with doses up to fourfold higher than the recommended dose
: Bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine and rupatadine

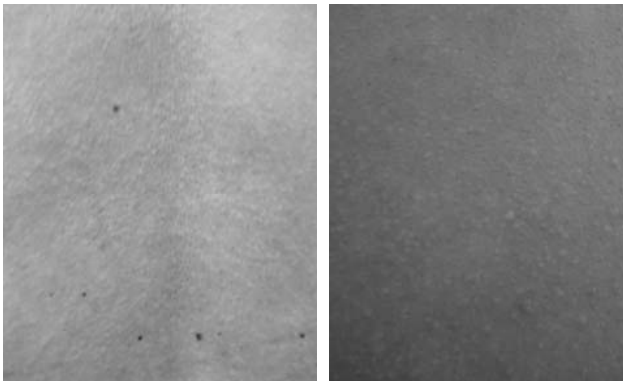
물리적 두드러기의 진단

질병	검사방법	양성소견
수인성 두드러기	30분 간 35°C의 물에 노출	해당 부위에 두드러기
콜린성 두드러기	운동 유발	전형적인 두드러기 발생
피부요기증	설압자로 피부를 압박	1~3분 이내에 압박한 부위에 두드러기 발생
지연성 압박 두드러기	무거운 물건을 어깨에 10~15분 간 걸어 놓음	4~12시간 이후에 혈관부종 발생
진동 두드러기	4분간 진동기(vortex mixer)에 노출	경계가 명확한 혈관부종 발생
한랭 두드러기	얼음조각에 5분간 노출	피부가 다시 따뜻해질 때 노출된 부위에 두드러기
일광 두드러기	특정 파장의 빛에 노출	해당 부위에 두드러기
운동 유발성 두드러기	운동	두드러기, 가려움증, 혈관부종 등 발생

피부요기증



콜린성 두드러기

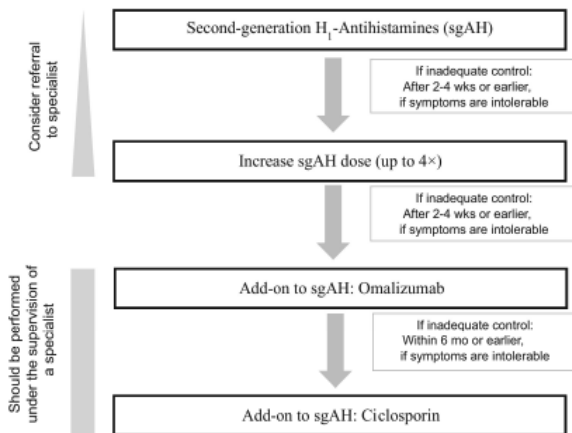


한랭 두드러기



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두드러기 표준치료



Steroids ?

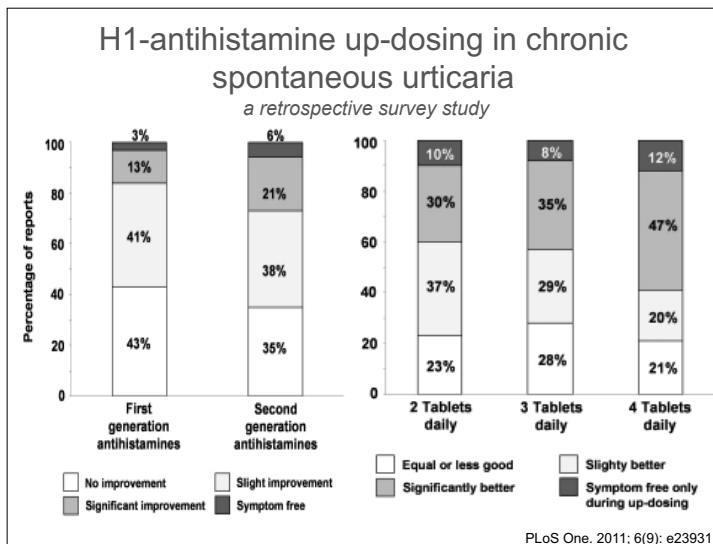
- nisolone is only licensed for acute urticaria). For acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids, that is treatment of a maximum of up to 10 days, may, however, be helpful to reduce disease duration/activity.^{136,137} Nevertheless, well-designed RCTs are lacking.

J Invest Allergol Clin Immunol. 2010;20(5):386-90

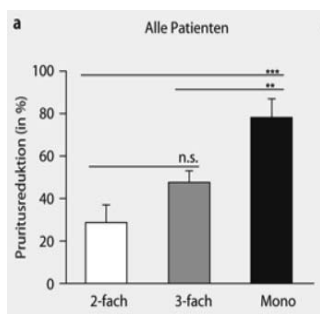
• Topical steroids

- Not helpful (with the possible exception of pressure urticaria on soles as alternative therapy with low evidence).

- Study showed benefit with doses up to fourfold higher than the recommended dose
- : Bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine and rupatadine



Up-dosing > Combination

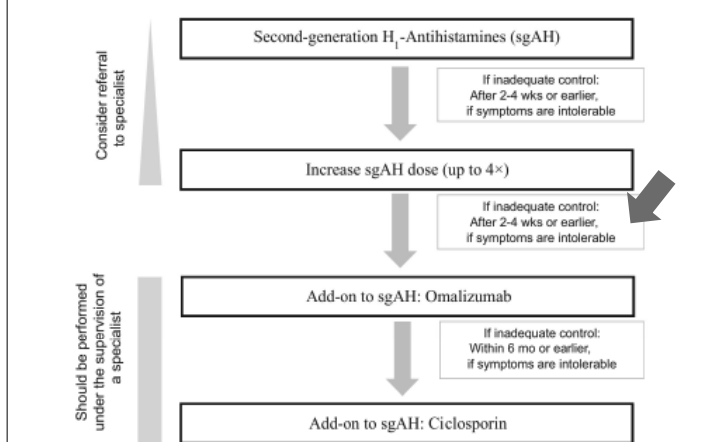


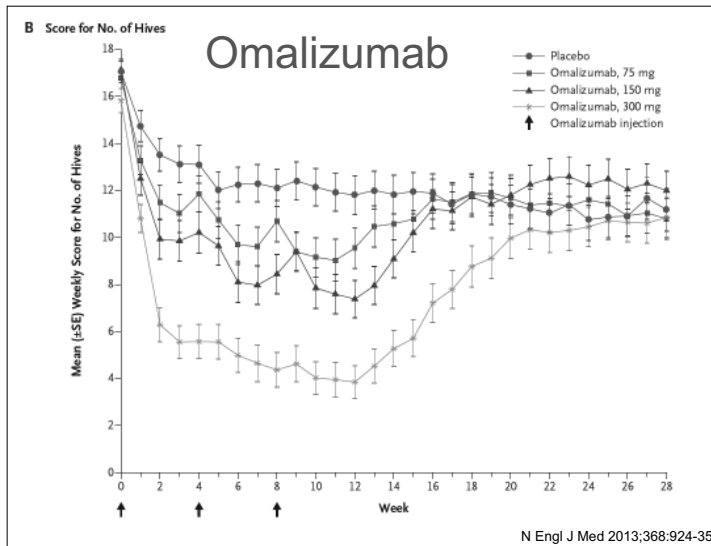
2-nsAH: levocetirizine 10 mg/fexofenadine 360 mg
3-nsAH: levocetirizine 10 mg/fexofenadine 360mg/azelastine 4 mg
Mono : desloratadine 20 mg per day.

Der Hautarzt 2009, 60(7); 564-568

EAACI/GA²LEN/EDF/WAO guideline Allergy, 2018

두드러기 표준치료





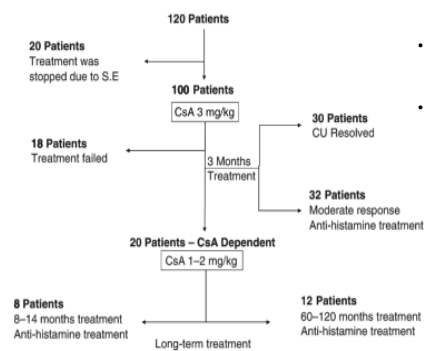
Cyclosporin

- Effective dose range : 3-5 mg/kg/day
- Treatment duration : 3-6 months
- Monitoring : BP, kidney function, liver function regularly
- Treatment response
 - 치료 중단 후 50%의 환자에서 9개월까지 complete remission 유지
 - 나머지 환자에서는 flare up의 감소와 항히스타민제에 대한 response 유지에 도움

Allergy Asthma Proc 2003;24:285-90.

Cyclosporin : long term treatment

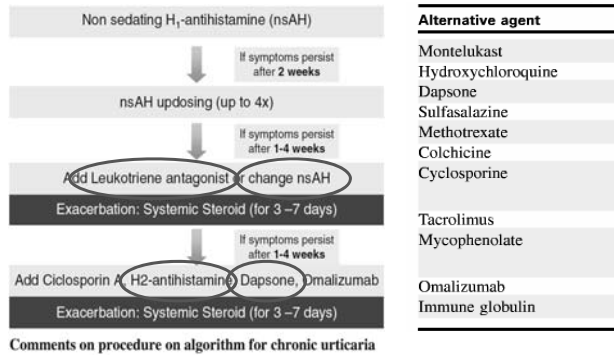
- 중단 후 재발 경향을 보이는 환자에서 수년간 유지



- Low-dose CsA improved CSU severity in most cases.
- 20% of patients need long-term treatment.

Allergy 2010 65: 1478-1482

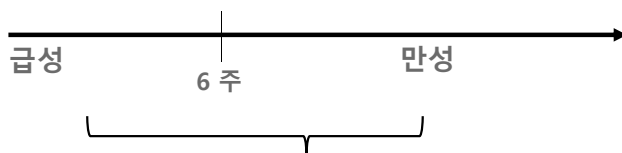
Other options



차 례

- **항히스타민제 치료에 효과 없을 때**
 - 두드러기 진단 확인
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두드러기의 분류



Different etiologies and prognosis

원인이 뭔가요? 급성 두드러기

Types	Subtypes	Extended diagnostic programme ^b (based on history) For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated	
		Routine diagnostic tests (recommended)	
Spontaneous urticaria	Acute spontaneous urticaria	None	None ^b
	CSU	Differential blood count, ESR and/or CRP	Avoidance of suspected triggers (eg, drugs); Conduction of diagnostic tests for (in no preferred order): (i) infectious diseases (eg, <i>Helicobacter pylori</i>); (ii) functional auto-antibodies (eg, autologous skin serum test); (iii) thyroid gland disorders (thyroid hormones and auto-antibodies); (iv) allergy (skin tests and/or allergen avoidance test, eg, avoidance diet); (v) concomitant CINDU, see below ⁴⁹ ; (vi) severe systemic diseases (eg, tryptase); (vii) other (eg, lesional skin biopsy)

^b Unless strongly suggested by patient history, for example allergy

Acute Urticaria

Ruth A. Sabroe, FRCP, MD

4.1 | Diagnostic work up in Acute Urticaria

Acute urticaria usually does not require a diagnostic workup, as it is usually self-limiting. The only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or the existence of other eliciting factors such as nonsteroidal anti-inflammatory drugs (NSAIDs). In this case, allergy tests as well as educating the patients may be useful to allow patients to avoid re-exposure to relevant causative factors.

KEYWORDS

• Acute urticaria • Anaphylaxis

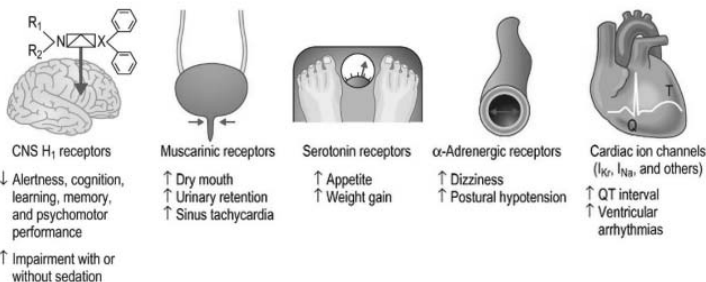
KEY POINTS




- Acute urticaria is common in adults and children.
- Acute urticaria is most often idiopathic, but it may follow infection, exposure to drugs, or less commonly food ingestion.
- Acute urticaria may be a presenting symptom of anaphylaxis.
- Acute urticaria by definition resolves within 6 weeks, but it often settles within 2 to 3 weeks. It may recur in a small proportion of patients.
- Acute urticaria may be treated with antihistamines or oral steroids if needed.

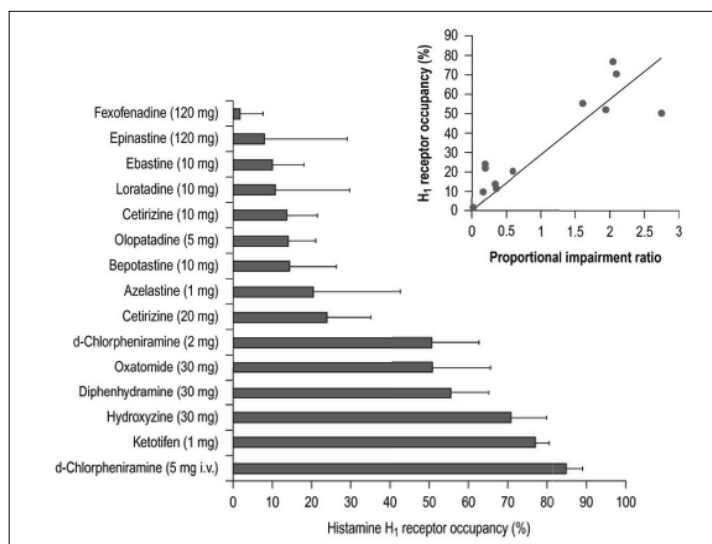
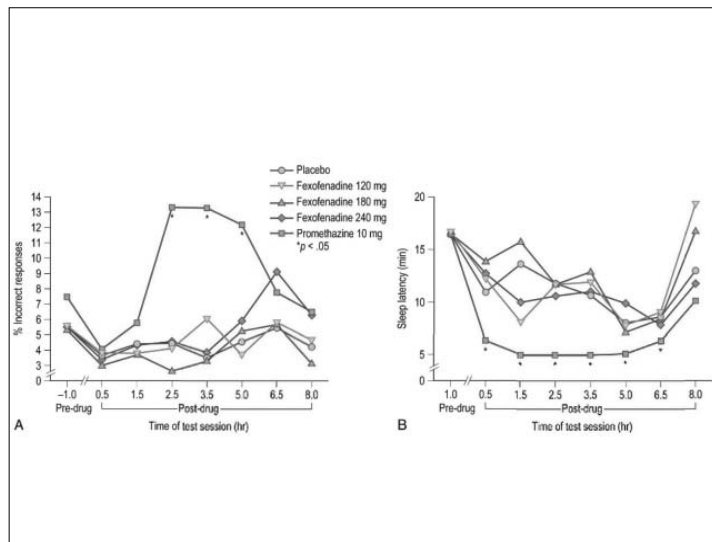
Immunol Allergy Clin N Am. 2014

항히스타민제 부작용

Potential Adverse Effects of First-Generation H_1 Antihistamines



Conditions Currently Treated with H ₁ Antihistamines		
Strong evidence base for second (new)-generation H ₁ antihistamine use	Weak evidence base for H ₁ antihistamine use	Weak evidence base for first (old)-generation H ₁ antihistamine use in CNS and vestibular disorders
 Allergic rhinitis	Atopic dermatitis Asthma Anaphylaxis Nonallergic angioedema Upper respiratory tract infections (colds)	Insomnia Conscious sedation Perioperative sedation Analgesia Anxiety Serotonin syndrome
 Allergic conjunctivitis	Otitis media Sinusitis Nasal polyps Nonspecific cough Nonallergic, nonspecific itching	Akathisia Migraine Motion sickness Vertigo
 Urticaria		



Fexofenadine

- P-glycoprotein *inducers*
 - Grapefruit juice, rifampin, and St. John's wort
 - Decrease fexofenadine absorption
- Glycoprotein *inhibitors*
 - Erythromycin and ketoconazole
 - Increase fexofenadine absorption
- Binds to aluminum/magnesium-containing antacids
 - Administration within 15 minutes of ingestion of these agents should be avoided

Hepatic CYP450 system

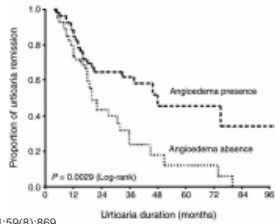
- All old-generation H₁ antihistamines
- New-generation H₁ antihistamines
 - Desloratadine and Loratadine
- Drug concentration ↑
 - by CYP inhibitors (= metabolism of drug ↓)
 - Erythromycin, azithromycin, and other macrolide antibiotics or ketoconazole and other imidazole antifungals.

원인이 뭔가요? 만성 두드러기

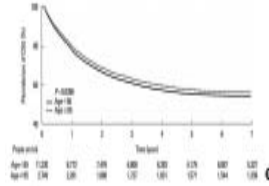
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만성두드러기

- 대부분 저절로 좋아짐
- 평균 유병기간: 2~5년
- 1년 이내에 사라지는 경우: 30~50%
- 5년 이상 지속 되는 경우: 약 20% 전후
- 증상이 심할수록 오래 지속되는 경향



Allergy. 2004;59(8):869



Allergy Asthma Immunol Res. 2018 Jan; 10(1): 83-

물리적 두드러기 예후

	Definition	Frequency*	Duration*
Symptomatic dermatographism	Itching and/or burning skin and the development of strip-shaped wheals due to shear force acting on the skin	1-5% in the general population (10, 139-141)	6.5 years with a great variance (142-144)
Cold Urticaria	Itchy wheals or angioedema after cold exposure of the skin	Up to one-third of all PhysU cases (145)	4.8-7.9 years (27, 28, 32)
Heat Urticaria	Itchy wheals after heat exposure of the skin	Very rare, no data available	Very rare, no data available
Delayed Pressure Urticaria	Erythematous skin swelling after the application of sustained pressure	37% of patients with CSU (64) but rare as a primary inducible urticaria	6-9 years (142, 146, 147)
Solar urticaria	Itchy wheals that occur after light (UV and/or visible light) exposure	Rare in general population, 0.08% of patients with CSU (75), 18% of patients who consult a hospital because of sunlight-related skin problems (147)	3-6 years (148-150)
Vibratory angioedema	Cutaneous swellings immediately after exposure to vibration	Very rare, no data available	Very rare, no data available
Cholinergic Urticaria	Itchy wheals after active or passive warming	4-11.2% of population (151-153)	4-7.5 years (154, 155)
Aquagenic urticaria	Itchy wheals or angioedema after skin contact with water	Very rare, no data available	Very rare, no data available
Contact Urticaria	Itchy wheals or angioedema after contact with eliciting agent	Variable, depending on elicitor	Variable, depending on elicitor

5 | MANAGEMENT OF URTICARIA

5.1 | Basic considerations

1. The goal of treatment is to treat the disease until it is gone.
2. The therapeutic approach to CU can involve
 - a. the identification and elimination of underlying causes,
 - b. the avoidance of eliciting factors,
 - c. tolerance induction, and/or
 - d. the use of pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators
3. Treatment should follow the basic principles of treating as much as needed and as little as possible. This may mean stepping up or stepping down in the treatment algorithm according to the course of disease.

만성 두드러기

While antihistamines at up to quadruple the manufacturers' recommended dosages will control symptoms in a large part of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. Before changing to an alternative therapy, it is recommended to wait for 1-4 weeks to allow full effectiveness.

As the severity of urticaria may fluctuate, and spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every 3-6 months.

5.2.6 | Dietary management

- **L** IgE-mediated food allergy is extremely rarely the underlying cause of CSU.^{84,89} If identified, the specific food allergens need to be omitted as far as possible which leads to a remission within less than 24 hours. In some CSU patients, pseudo-allergic reactions (non-IgE-mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases to food additives have been observed.^{84,89-93} A pseudoallergen-free diet, containing only low levels of natural as well as artificial food pseudoallergens, has been tested in different countries⁹⁴ and also a low histamine diet may improve symptoms in those patients.⁹⁵ Those diets are controversial and as yet unproven in well-designed double-blind placebo-controlled studies. However, when used, they must usually be maintained for a minimum of 2-3 weeks before beneficial effects are observed. However, it should be pointed out that this kind of treat-

Dairy products
cream, butter
soured milk,
cheese

Fish (fresh)
cod, salmon, cod
perch

**Sweets and
gums, chocolate**

**Fruits: orange,
strawberries,
bananas, kiwi**

**Cereals/Past
products, pasta,
couscous, grains
(buckwheat)**

Mean
value
(4.92)
0.50
0.50

J Eur Acad Dermatol Venereol. 2016 Sep 13.

만성 두드러기 치료

• Basic considerations

- ✓ 두드러기 치료 목표는 증상이 완전히 조절될 때까지 치료하는 것이다.
- ✓ 두드러기의 치료 접근법은 다음과 같은 것들을 포함해야 한다.
 - 기저 원인 파악, 제거
 - 약화 인자 제거
- ✓ 필요한 만큼 충분히 길게, 가능한 낮은 단계로 치료해야 한다.