



# **Cold urticaria in children. How dangerous is it?**

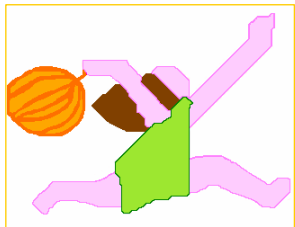
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# Definition

Cold urticaria is a disorder characterized by the rapid onset of pruritus, erythema, and swelling after exposure to a cold stimulus

# Epidemiology

- Any age group (more common 18-25yo)  
Female predilection 2:1
- Incidence: 0.05%  
Frequency between physical urticarias: 5.2-33.8%  
(higher in regions with cold climate)
- 4<sup>th</sup> commonest type of chronic urticaria  
(chronic spontaneous, dermographism, cholinergic urticaria)
- Atopy is common

# Pathophysiology I

- *in vitro* cold-dependent release of histamine from skin biopsies and *in vivo* histamine release in serum after immersing an arm into cold water (Figure)

Kaplan A. NEJM 1981

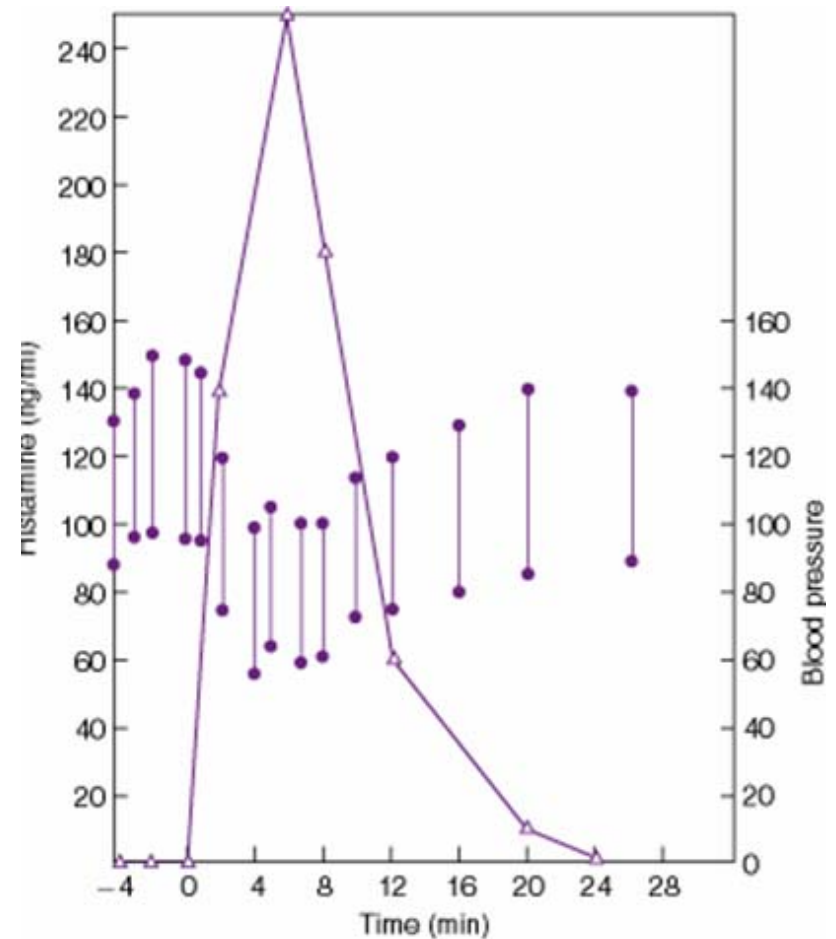
Kaplan A. JACI 1975

- Basophils do not release histamine  
→ cutaneous mast cells essential

- **cold-transformed antibody plus normal skin antigens reaction**

**and/or**

**cold-induced skin antigen plus normal antibody reaction?**



# Pathophysiology II

- Infections (respiratory tract, urogenital tract, oral cavity)
  - Viral (HAV, HBV, HCV, HIV, EBV, HSV, )
  - Bacterial (H.pylori, borrelia *sp*, mycoplasma pneumoniae)
  - Parasites (toxoplasma *sp*)
- Cold-dependent abnormal immunoglobulins
  - cryoglobulins, cryofibrinogens, cold agglutinins
  - Donath-Landsteiner antibody
- Hymenoptera stings

**No definite causative relationship has be determined**

# Triggers

- Cold air (cold/windy weather, air-condition)
- Cold surfaces, objects (handling, touching)
- Cold fluids
- Ingestion of cold foods and liquids
- Aquatic activities
- Restriction of blood flow (e.g. typing)

# Clinical manifestations I

- Urticarial lesions usually limited to cold-exposed skin areas
- Patients may experience severe systemic and anaphylactic reactions
- Severity depending on
  - the sensitivity of the patient
  - the potency/degree of the cold stimulus and
  - the duration of the cold stimulus
- Local potentially fatal reactions
  - occlusive oedema
    - of the pharynx due to cold drinks,
    - of the upper airways due to cold air





# Clinical manifestations II

- **Skin**→ urticaria, angio-oedema
- **Oropharynx**→ swelling of the lips, tongue, uvula, pharynx
- **Lower respiratory tract**→ wheezing, hoarseness, dyspnoea
- **Gastrointestinal system**→ nausea, vomiting, stomachache, abdominal cramps
- **Cardiovascular system**→ tachycardia, hypotension
- **Central nervous system**→ headaches, disorientation, unconsciousness

# Grading severity

- **Type I:**  
localized urticaria/angio-oedema
- **Type II**  
≥1 episode of generalized urticaria / angio-oedema ±  
involvement of a second system  
(excluding cardiovascular system)
- **Type III:**  
severe systemic reactions with  
≥1 episode of generalized urticaria/angio-oedema  
associated with hypotension or coherent symptoms  
(dizziness, fainting, disorientation, syncope)

# Guidelines

- **British guidelines** **C.E.H. Grattan et al. BJD 2007**
  - Acquired cold contact urticaria
    - *...application of melting ice cubes in a plastic bag to the skin for 20 min*  
*...local rapid wealing after re-warming the skin*
    - *...if negative, an arm can be immersed in cold water at 5-10°C for 10 min*
  - Reflex cold urticaria
    - *Only generalized cooling of the body induces weals and ice-cube test is negative. Wealing can be provoked by cooling the body in a room at 4°C for 30 min.*
- **EAACI / GA<sup>2</sup>LEN / EDF guidelines** **T. Zuberbier et al Allergy 2006**
  - *...cold provocation and threshold test*

# Diagnosis I



## Ice-cube test

- Cold Stimulation Time Test (CSTT)

## Hand immersion test

- cold water  
at 5-10°C  
for 10'

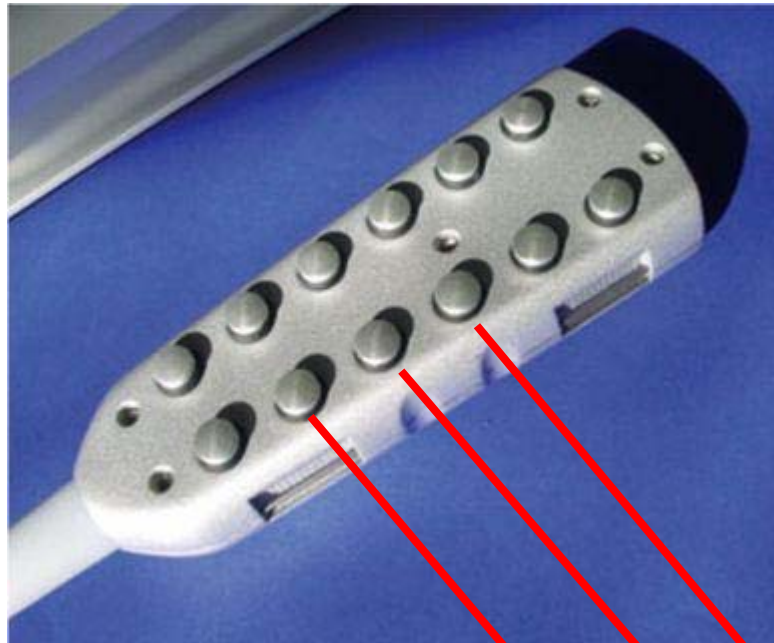
**Caution: systemic reactions may occur**

Wanderer A. JACI 1990



# Diagnosis II

- TempTest<sup>®</sup>  
standardized cold provocation testing



Thermal elements

# Diagnostic Classification

- **Acquired Cold Urticaria (ACU)** with a positive CSTT
  - Primary ACU
  - Secondary ACU
    - cryoglobulinemia
    - infectious diseases
    - leukocytoclastic vasculitis
  - Miscellaneous
    - insect stings
    - drugs
    - neoplasms
- **Atypical ACU** atypical responses to CSTT
  - Systemic ACU
  - Cold-dependent dermographism
  - Cold-induced cholinergic urticaria
  - Delayed cold urticaria
  - Localized cold urticaria
  - Localized cold reflex
- **Hereditary Subtypes**
  - Delayed cold urticaria (autosomal dominant)
  - Familial cold auto-inflammatory syndrome (autosomal dominant)

# Diagnostic Evaluation

- Historical or physical evidence of acquired cold induced wheals or angio-oedema
- Positive provocation (cold stimulation) test
- CSTT (and temperature thresholds)
- Negative evidence of underling diseases

# Examinations

- Differential blood count
- Erythrocyte sedimentation rate (ESR)
- C- reactive protein (CRP)
  
- Cryoglobulins, cryofibrinogens, cold agglutinins
  - $\approx 4\%$  of cold urticaria patients may have cryoglobulinemia  
*Koeppel MC et al. Ann Venereol 1996*
  - 3% of patients with cryoglobulinemia may have cold urticaria  
*Dammacco F et al. Eur J Clin Invest 2001*



# Demographics in children

- Age of onset: 7yo (range 0.5-14.5yo)
- Aquatic activity: the most common trigger
- 1 out of 3 had anaphylactic reactions
- 1 out of 4 had experienced hypotension
- 84.2% sensitized to common allergens

# Prognosis: Duration

- The course tends to be chronic
- Mean duration ranges from 4.8 to 9.3 years
- The disease resolves (**Van Der Valk PGM et al. BJD 2002**)
  - within 5 years in 11%
  - within 10 years in 26%
- Most patients experience symptoms for years regardless of the age of onset
- There is no definite method/test/parameter to predict the duration

**Wanderer A et al. JACI 1987**

**Mathelier-Fusade P et al. Arch Derm 1998**

**Möller A et al. Hautarzt 1996**

# Prognosis: Risk factors I

- reported clinical reactions to natural cold exposure
- **sensitivity** of the individual
- trigger's **temperature** (inverse relation) and
- **time of exposure** (proportional relation)

# Prognosis: Risk factors II

- **CSTT**
- **oropharyngeal reactions**
- **aquatic activities**

Gorevic P, Kaplan AP. Int J Dermatol 1980;19:417

# Probability of anaphylaxis

- **20 children with ACU**
  - 10/20 localized or generalized urticaria
  - 10/20 anaphylaxis
  - 15/20 sensitized to at least common allergen
- **CSTT**
  - 3,2±1,5'** (+) history of anaphylaxis
  - (p-value= 0.030)
  - 7,7±5,9'** (-) history of anaphylaxis
- **CSTT 6 min → threshold**

# Treatment I

- Management is based on identification of the
  - triggers
  - specific temperature and
  - exposure time
- Antihistamines (up to x4 the daily recommended dose)

**Siebenhaar F et al. JACI 2009**
- Emergency medication kit for cases with anaphylaxis
  - Epinephrine
  - Antihistamines

# Treatment II

- Leukotriene receptor antagonist  
Bonadonna P et al. J Am Acad Dermatol 2003
- Ciclosporin  
Marsland AM, Beck MH. Br J Dermatol 2003
- Corticosteroids  
Black AK et al. Br J Clin Pharmacol 1980
- Anti-IgE treatment  
Boyce JA. JACI 2006
- A trial of high-dose penicillin or doxycycline  
Siebenhaar F et al. CED 2007
- Tolerance induction  
Black AK et al. Lancet 1979

# Recommendations

- Children should supervised by someone trained how to use epinephrine autoinjector
- Pretreatment with an antihistamine is recommended
- There are no data suggesting that antihistamines administration in individuals with anaphylaxis prevent systemic reactions
- Higher temperature water (swimming pool vs sea) may still induce reactions
- Avoidance of exposure to cold stimuli is the cornerstone to prevention



# Conclusions

- Cold urticaria is uncommon in children and mostly idiopathic
- There is a higher rate of atopy and family history of atopy
- Systemic reactions are common and anaphylaxis occur in 1 out of 3 patients
- CSTT provides important clinical information for the severity and the management of cold urticaria
- Prognosis (evolution, remission) is unknown