Chronic Urticaria and Angioedema in Adults

Selected Topics in Internal Medicine
Review Course

Internal Medicine Department
University of Puerto Rico
School of Medicine

Fernando J Lopez-Malpica, MD
Professor


Hives
A.D.A.M.


A.D.A.M.


A.D.A.M.

Idiopathic Urticaria

Diffuse
“Giant” Hives

Idiopathic Angioedema

Idiopathic? Definitions…

- Occurring without known cause.
- When the cause of a disease or process is not known.
- Of a condition or disorder that occurs spontaneously for unknown reason.
- Arising spontaneously or from an obscure or unknown cause.
- With no known cause.
- Applied to a medical problem or disease when the cause is unknown.
- Describes any disorder with unknown causes.
- Referring to a disorder of unknown cause.
- Of unknown cause or explanation.
- Occurring spontaneously, not traceable to a direct cause.
- Etc…

Is urticaria an idiopathic condition?

- Lessons learned from other illnesses or *maladies*
  - *Periarteritis nodosa* and Hepatitis B virus
  - Peptic ulcer disease and *Helicobacter pylori*
  - Viral illnesses, aspirin and Reyes Syndrome
  - Guillain-Barre Syndrome and *Influenza* infection
  - Burkitts Lymphoma and EBV infection
- Infections and autoimmune and malignant diseases…

Urticaria

USA

- Overall, urticaria is reported to affect as many as 25% of people at some point in their lives. True incidence of CIU is unknown; however, it is believed to occur in 0.1-3% of the population

International

- The incidence is the same as in the United States.

Urticaria-Quality of Life

Mortality/Morbidity

- Unlike angioedema, which may affect the airway, urticaria is not a life-threatening disease; however, chronic urticaria has been shown to have a negative impact on the quality of life of affected patients. The effects of chronic urticaria on the activities of daily living, social interactions, rest, and work were found to be similar to those experienced by patients with heart disease.

Age

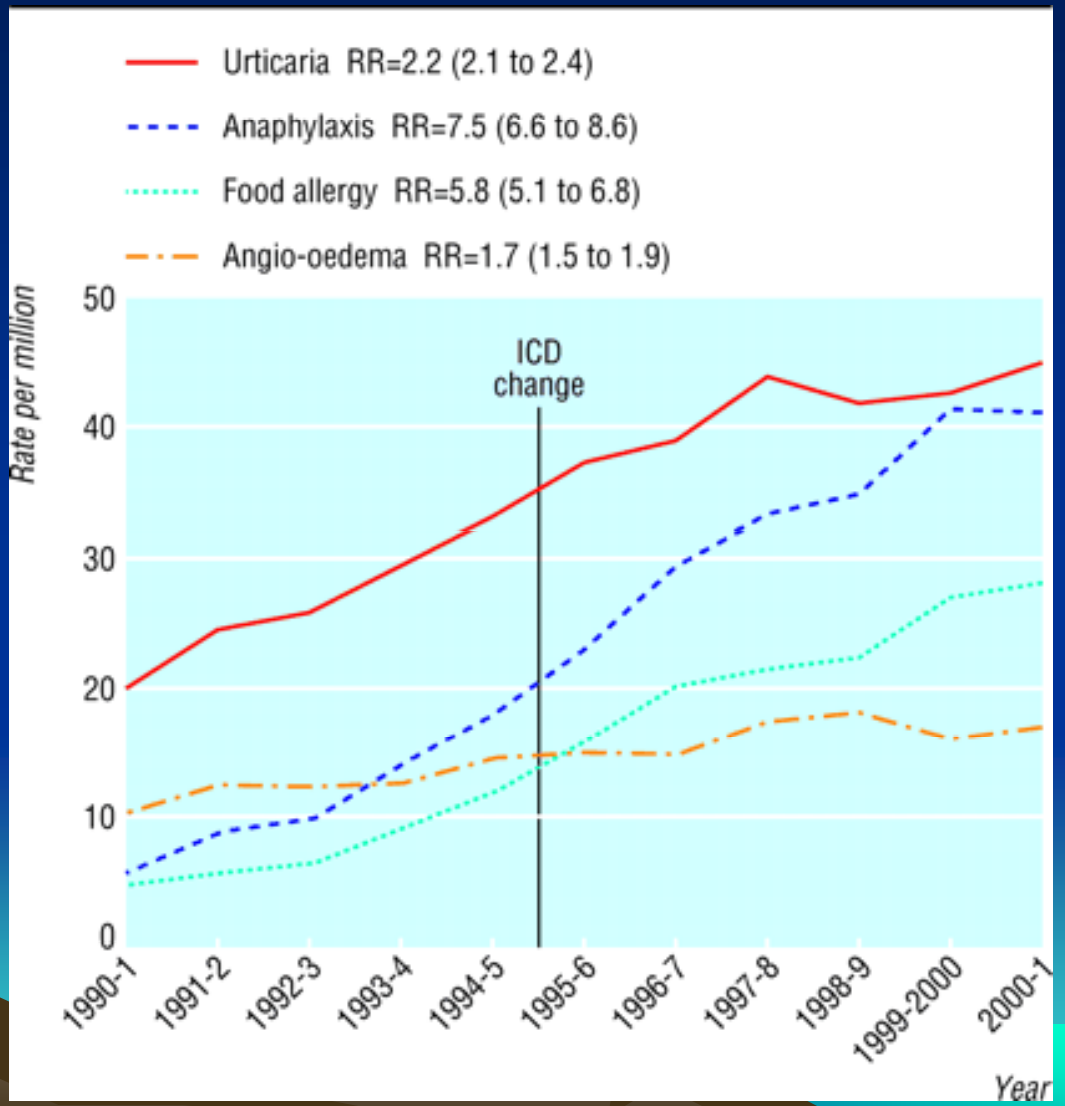
- Chronic urticaria is reported to be more common in older adults, while acute urticaria is more common in children.

Sex

- CIU occurs twice as often in women than in men.

Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data

British Medical Journal 327:1142-1143 (15 November 2003)



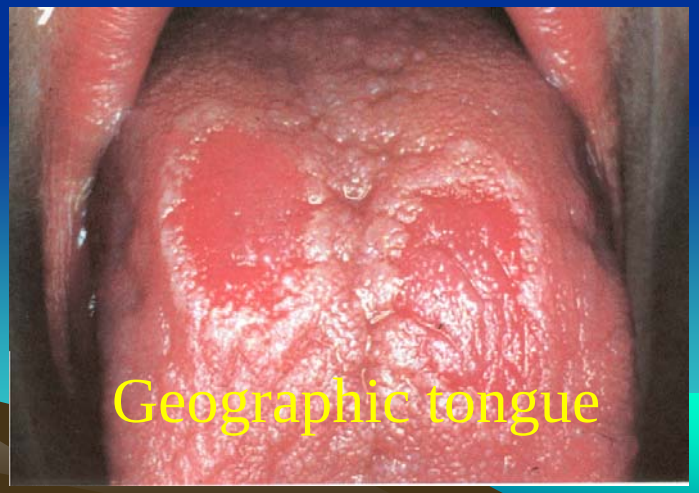
Case Study of Chronic Urticaria
Urticaria and Dermatographism in an Adult

Case Study of Chronic Urticaria
Urticaria and Dermatographism in an Adult

- This 43 y/o male is suffering from hives for more than 13 months. Has visited at least 4 dermatologists and although he improves with the use of antihistamines they make him sleepy. He has had nasal allergies all his life and asthma as a child.

Case Study of Chronic Urticaria
Urticaria and Dermatographism in an Adult

- When his skin is traumatized a hive develops.
- Has been unable to identify any precipitating factor, except for above.
- His tongue is peculiar and has been described as “geographic” by some observers.



Geographic tongue

The patient asks…?

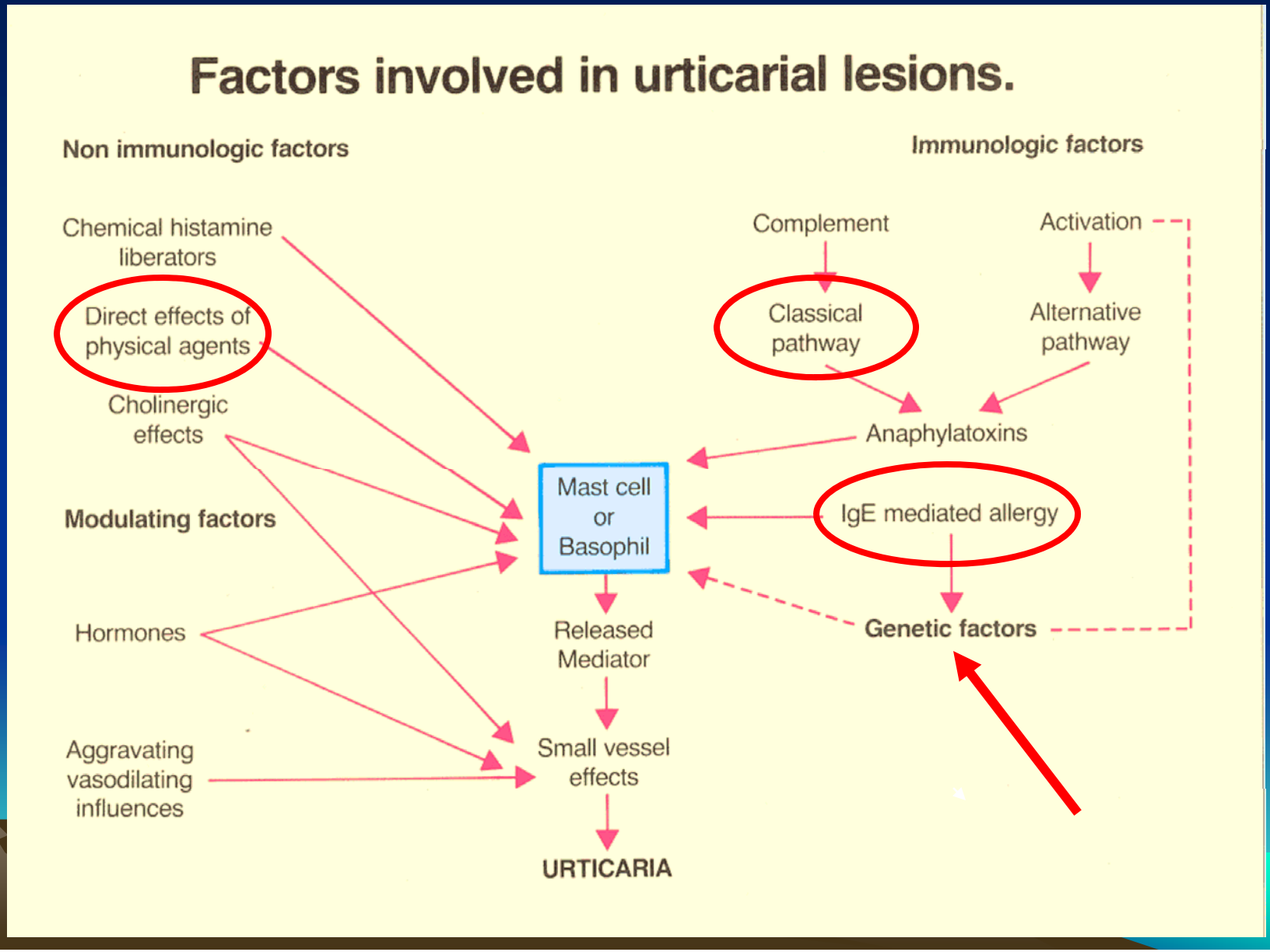
- Doctor, can you find what is going wrong with me?
- Is this is something bad, like cancer, or AIDS?
- I will do anything that you suggest. What I have to do to get better?
- I'm very depressed. This is affecting my intimate relations with my wife.
- ***Do you think I should consult a naturopath?***

Causes of urticaria/angioedema in adults…

- Allergies
- Autoimmune
- Physical
- Others…

So…History taking skills are of uttermost importance to properly guide workup and treatment!

The Urticaria "Syndrome"

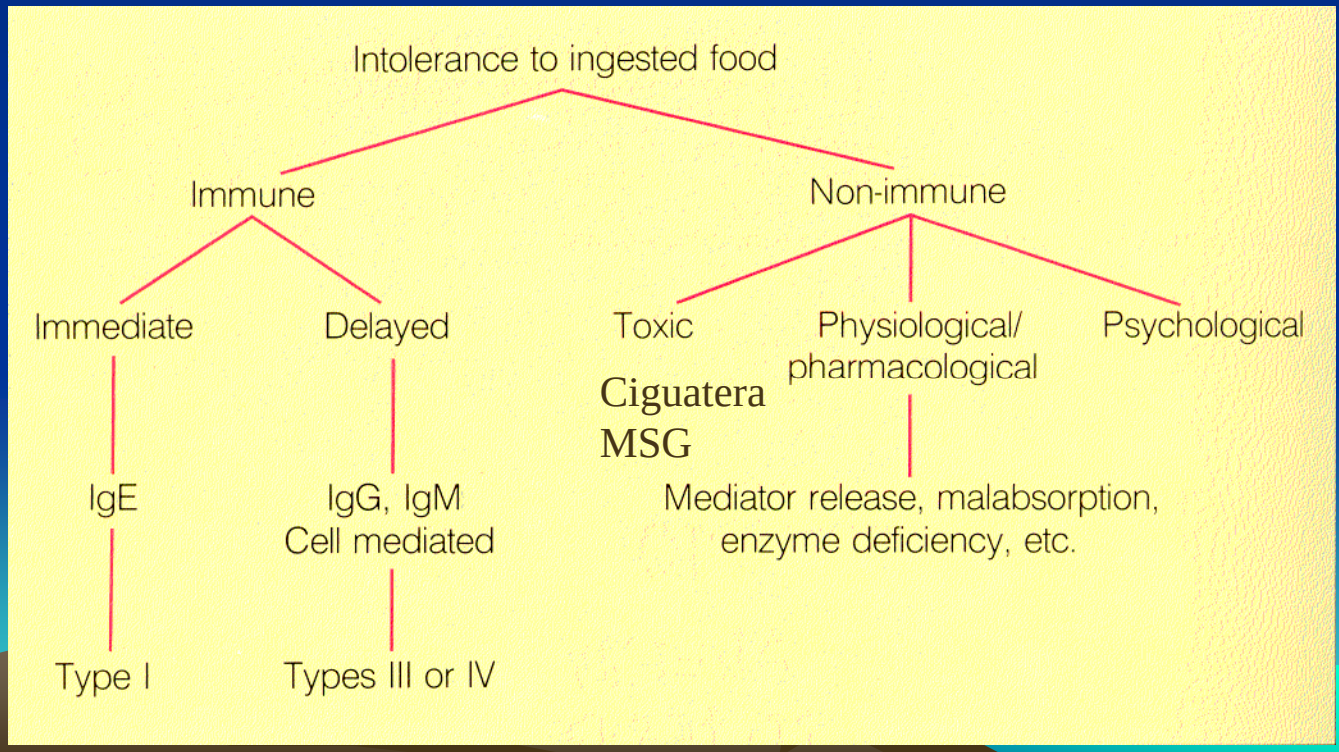


Potential Causes of Urticarial Reactions

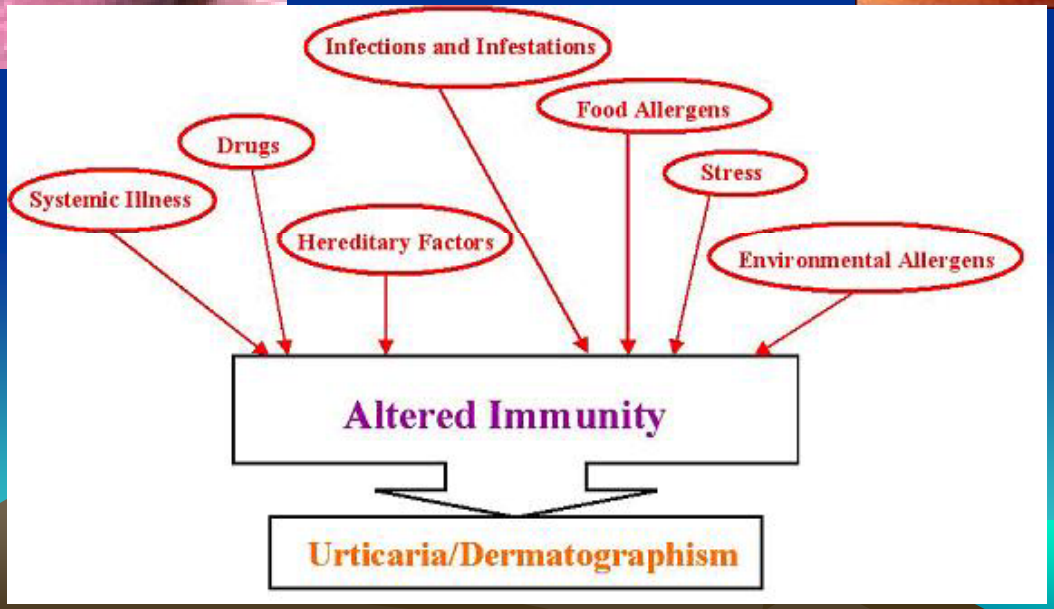
- Allergies
  - Foods
  - Medications
  - Inhalants (?)
  - Insect bites and stings
- Malignancies
- Infections
- Reactions to medications
- Autoimmunity
  - Autoantibodies to thyroid antigens,IgE and IgE receptors
- Physical agents
  - Cholinergic, heat, cold, pressure, vibration, water, solar-UV
- Psychological factors
- Exercise

Foods can trigger different types of reactions

(allergy being one of them!)



“Geographic” tongue and dermatographism



Common foods that can produce chronic urticaria symptoms

- Milk
- Chocolate
- Wheat
- Corn
- Eggs
- Pork
- Soy

Consider medications…!

Specifically-ACE metabolic pathway modifiers, NSAIDS, injectables as insulin, antibiotics, chemotherapeutics…

Cilinical Value of Elimination Diet in Chronic Urticaria

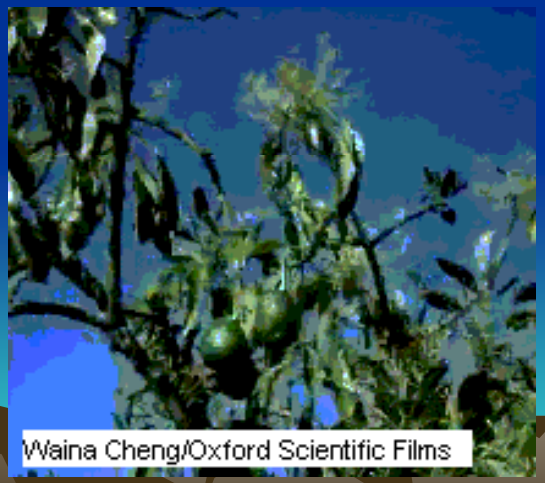
- “Wash out” period of 5 days in a limited, hypoallergenic diet and, if possible, free of medication
- Add one food or medication q 2 days
- Observe
- Challenge and rechallenge!

Role of House Dust Mite in Chronic Urticaria

- Possible association(?)
- Use of house dust avoidance measures(?)
- Use of specific inmunotherapy(?)

Latex Sensitivity in Chronic Urticaria

Occupational disease common in health care workers



Latex antigens cross reacts with some foods!

Physical Urticarias

- Commonly identified etiologies of chronic urticaria (approximately 20% of cases).
- Diagnosed by challenge testing.
- Several types exist, and it is not uncommon for a single patient to have more than 1 type.
  - Dermatographism/dermographism - Firm stroking
  - Delayed pressure urticaria
  - Cold urticaria
  - Aquagenic urticaria
  - Cholinergic urticaria - Heat, exercise, or stress
  - Solar urticaria
  - Vibratory urticaria

Aspirin and NSAID Sensitivity
Treatment Alternatives

- Acetaminophen
- Choline magnesium trisalicylate (Trilisate)
- Salsalate (Disalcid, Mono-Gesic, Salflex)
- Salicylamide
- Usually well tolerated!

- **ASA desensitization may be considered for the treatment of rheumatic or cardiovascular diseases**
- **Use of leukotrine receptors blockers and antagonists**

Case presentation

- A 40 y/o female has recurrent episodes of urticaria and angioedema involving mouth and tongue for 6 months. No respiratory difficulty nor hoarseness have been noted. There is a strong family history of thyroid disease. She has normal thyroid function tests but very high antithyroid Ab titers.

Systemic Diseases Associated with Urticarial Eruptions

- Hyperthyroidism, hypothyroidism
- Systemic lupus erythematosus
- Serum sickness, cryoglobulinemia
- Juvenile rheumatoid arthritis (JRA)
- Vitiligo
- Insulin dependent diabetes mellitus
- Pernicious anemia
- Infections
- Neoplasms
- Mastocytosis

Autoimmune Disease and CU in Adult Patients in Lithuania

- 101 patients , 82 females, median 43 y/o
- Abnormal findings
  - ↑ serum Ig E - 31 patients, 5 of them to inhalants
  - Specific IgE to foods were negative in pts with ↑ IgE
  - ↑sed rate- 2 pts
  - Total Ig G,M,A were unremarkable
  - + ANA – 4 pts.
  - ↑ Thyroid peroxidase – 30 pts
  - Autologous serum skin test (anti IgE or FcεRI Ab) - 33 pts
  - Sensitivity to NSAIDs – 9 pts

Most common cause of CU is autoimmunity

- 1/3 has autologous serum skin test (anti IgE or anti FcεRI Ab) or thyroiditis

Urticaria Autoantibodies

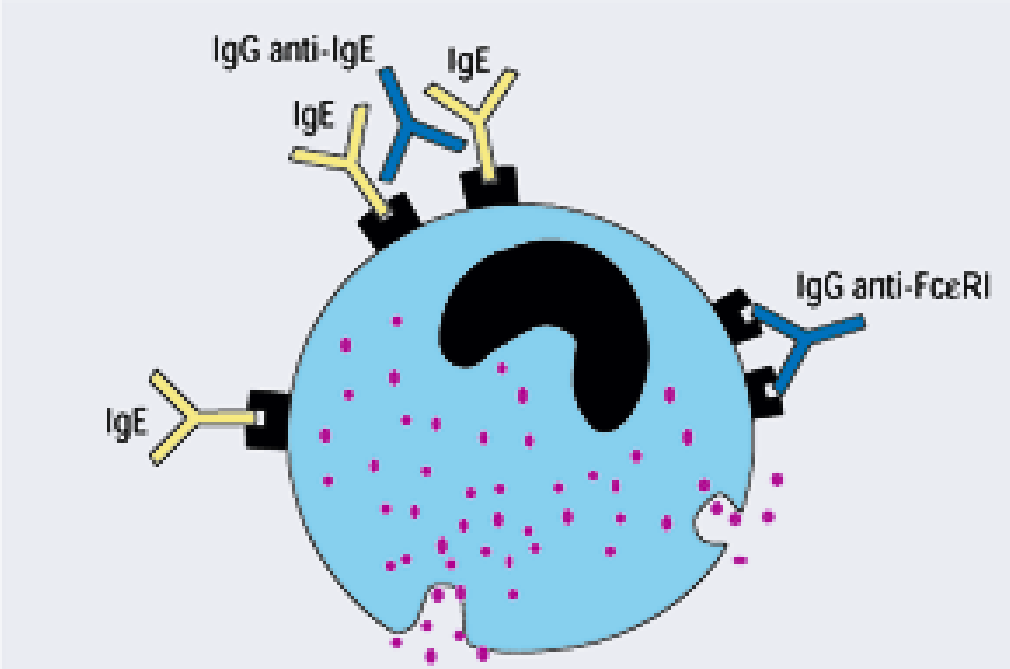


Figure 2. Autoantibodies on a mast cell in chronic urticaria. IgG antibodies to FcεRI or IgE cause cross-linking of these receptors or antibodies on mast cells, resulting in degranulation. Black, notched membrane structures represent a chain of the FcεRI expressed on the surface of dermal mast cells. IgG anti-FcεRI, IgG antibody to high-affinity IgE receptor; IgG anti-IgE, IgG antibody to IgE.

Reprinted, with permission, from Greaves.[1]

Anti FcεRI Testing in Chronic Urticaria

- Commercially available, + in 35-50% of CIU patients
  - Chart review Jan August 2007, 11 patients
  - 6/11 (+) for anti FcεRI -Chronic Autoimmune Urticaria (CAU)
    - 4/6 asymptomatic in standard treatment
    - 2/6 symptomatic
  - 5/11 (–) for anti FcεRI-Chronic Idiopathic Urticaria (CIU)
    - 3/5 improved with Std Tx
    - 2/5 resistant to multidrug Tx

Limited use in predicting response to Tx

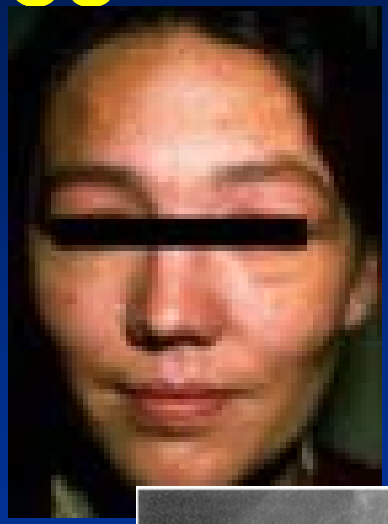
Identify who needs novel immunomodulators

A Alexis, et al, Albert Einstein, NY,
AAAAI Meeting,3-2008

Assesing Clinical Value of Elevated IgE Receptor Antibody Titers (FcεRI)

- Retrospective chart review - **708.1,8,9**
- Association of anti FcεRI Ab with other autoantibodies or other clinical measures of control
- FcεRI were **not** associated with clinical control or other autoantibodies
- Practical value of this test needs prospective studies

C1q Esterase Inhibitor Deficiency Syndromes



Case presentattion

24 y/o with regular bouts of abdominal pain and non pruritic angioedema since childhood. Symptoms get worst during her menstrual period. There are other family members with similar events. ANA is positive(1:160), speckled pattern, C4 is low and serum total IgE is normal.

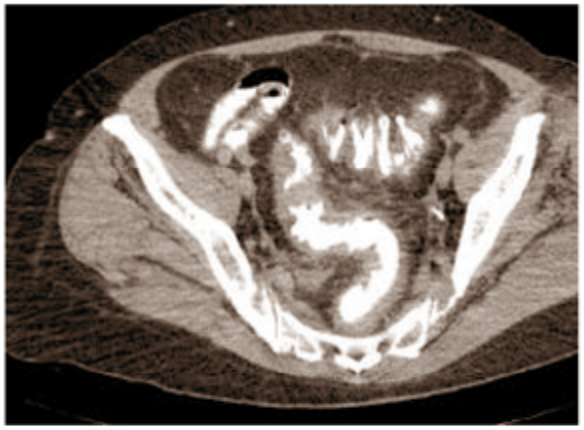


Figure 1—Inflammation of the colon. Abdominal CT scan with contrast showing pancolitis.

Classification of Hereditary and Acquired Angioedema*

C1q esterase INH abnormalities

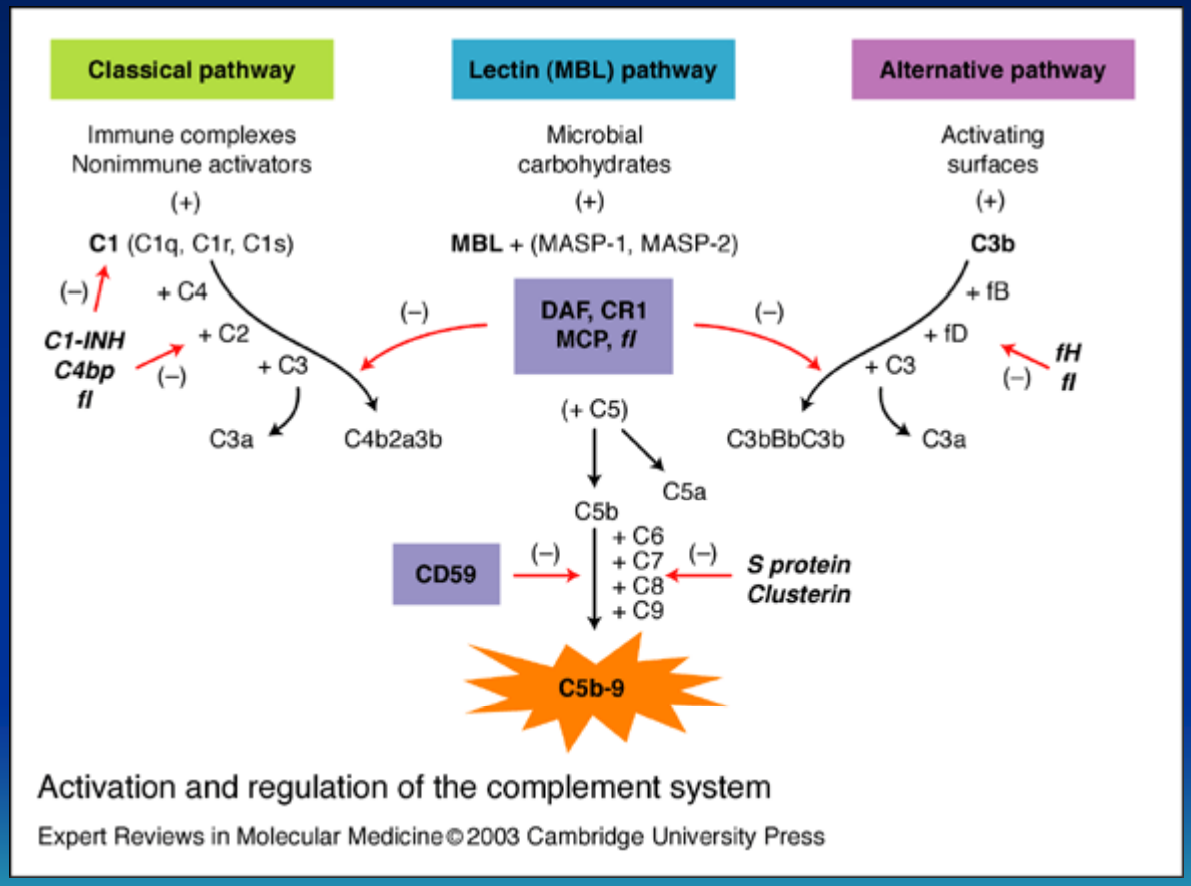
Hereditary forms of angioedema

- HAE-I: A mutation in C1-INH gene, absent or low antigenic and functional
- HAE-II: Mutations C1-INH gene usually causing normal antigen, reduced enzymatic activity and a low functional C1-INH
- Estrogen-dependent and estrogen-associated inherited angioedema (previously called HAE-III):The disease is either dependent on or associated with increased estrogen levels, only during pregnancy or with hormone therapy

Acquired forms of angioedema

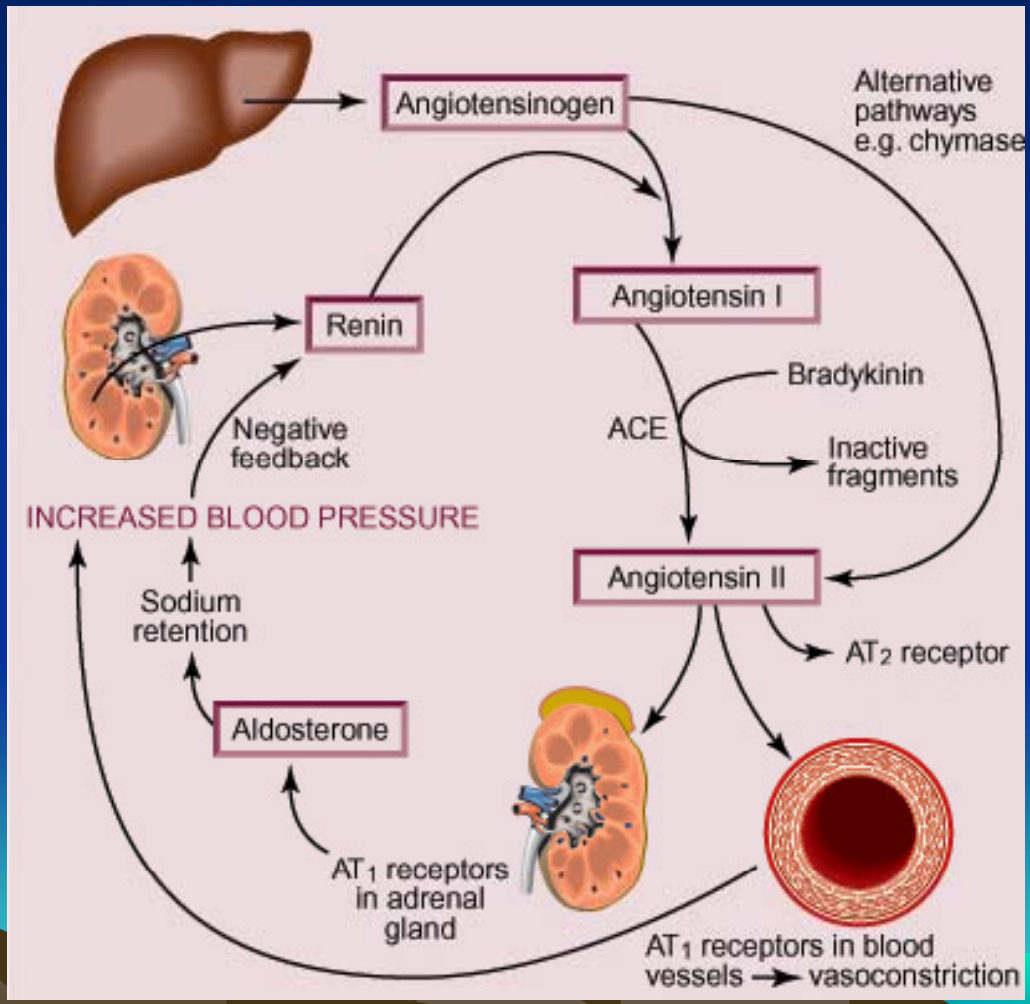
- Acquired C1-INH deficiency type I (AAE-I): Usually paraneoplastic, increased consumption or development of autoantibodies that impair the C1-INH function, enhancing cleavage of C1-INH
- Acquired C1-INH deficiency type II (AAE-II): Associated with autoimmune disease
- Angioedema in association with sex hormone changes: Female patients with angioedema associated with estrogen changes;
- Angiotensin-converting enzyme inhibitor or receptor blocker associated angioedema
- Other drug-induced angioedemaldiopathic angioedema

Complement System Activation

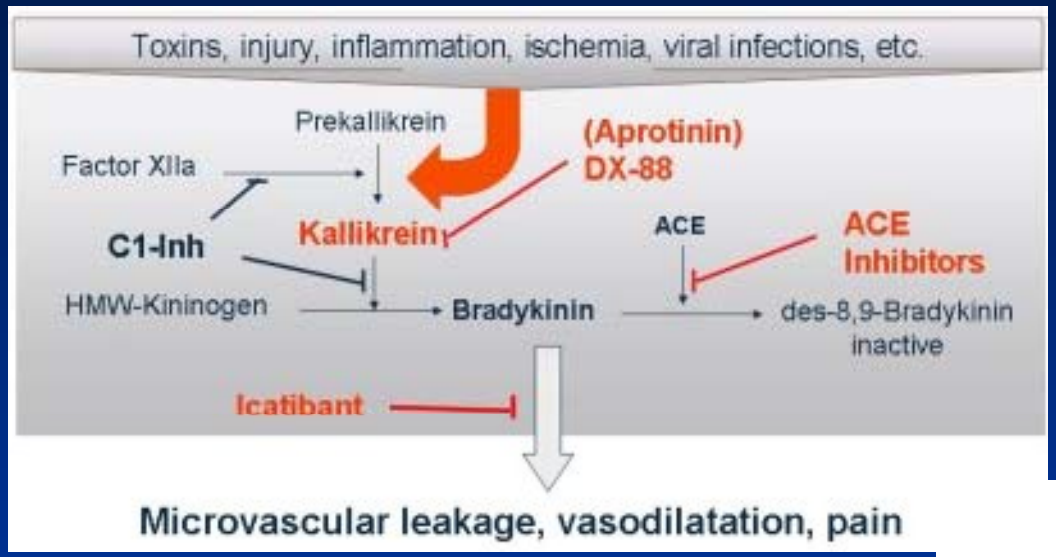


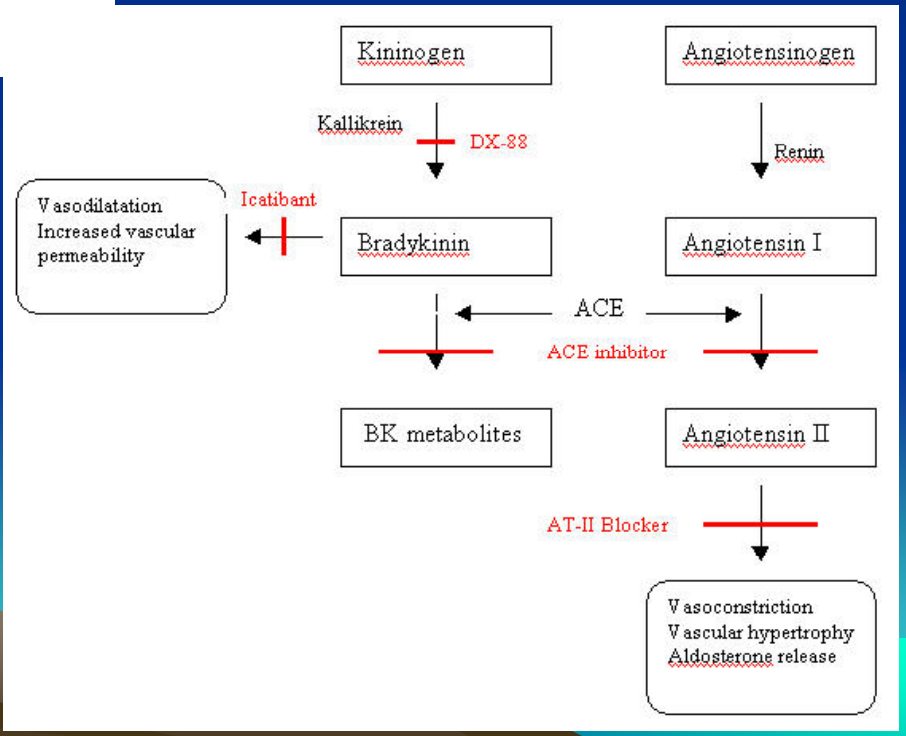
Activation and regulation of the complement system

Angiotensin-Bradykinin Systems Interactions



ACE inhibitor-induced angioedema.





Increase Hospitalizations due to HAE in the USA

- Review of 1998-2005 hospital database in USA
  - 1998- 3.3/100,000
  - 2004- 4.2/100,000
- Arterial hypertension diagnosed in most angioedema hospitalizations
- Also related to
  - Age -Ethnicity (african american)
- 24% of hosp. for angioedema were coded for adverse effects due to cardiovascular agent or antihypertensive Tx
- Angioedema hosp. in recent years related to increase of ACE inhibitors

Prodromal Signs and Symptoms Associated with HAE

- *-Erythema marginatum-* like rashes
- -Fatigue
- -Flu like symptoms
- -Hyperactivity
- -Localyzed tingling, thignesss and pain
- -Urticaria
- -Malaise
- -Irrritability, mood changes
- -Thirst
- -Nausea

- Duration-7 minutes to 4 days
- Prodromes are highly variable in prevalence, reproductibility,and duration

JC Kemp, et al, Penn State Coll Med,
AAAAI Meeting, 03-08

Safety of Fresh Frozen Plasma in HAE

- Chart review 1990->
- 76/82 (93%) demostrable improvement
- No adverse effects to FFP infusion
- In 3/5 cases FFP was sucessful as a prophylactic agent before surgery

M Prematta, et al,PennState Univ,
AAAAI Meeting, 03-08

Replacement Tx with C1 INH in Pregnant Women

- Observation 1995-97, 34 pregnancies in 22 women
- Attacks increase during pregnancy
  - From 12 attacks/ year to 48 attacks/year
- CI INH infussed as seemed necessary by patient
- No abortions, no malformations

W Kremp, et al, Goethe Uni, Frankfurt,
AAAAI Meeting, 3-2008

Novel Treatment of HAE

- *Icatibant*- Bradykinin B2 receptor antagonist
- *Ecallantide*- Plasma kallikrein inhibitor
- *Warfarin*- steroid sparing agent

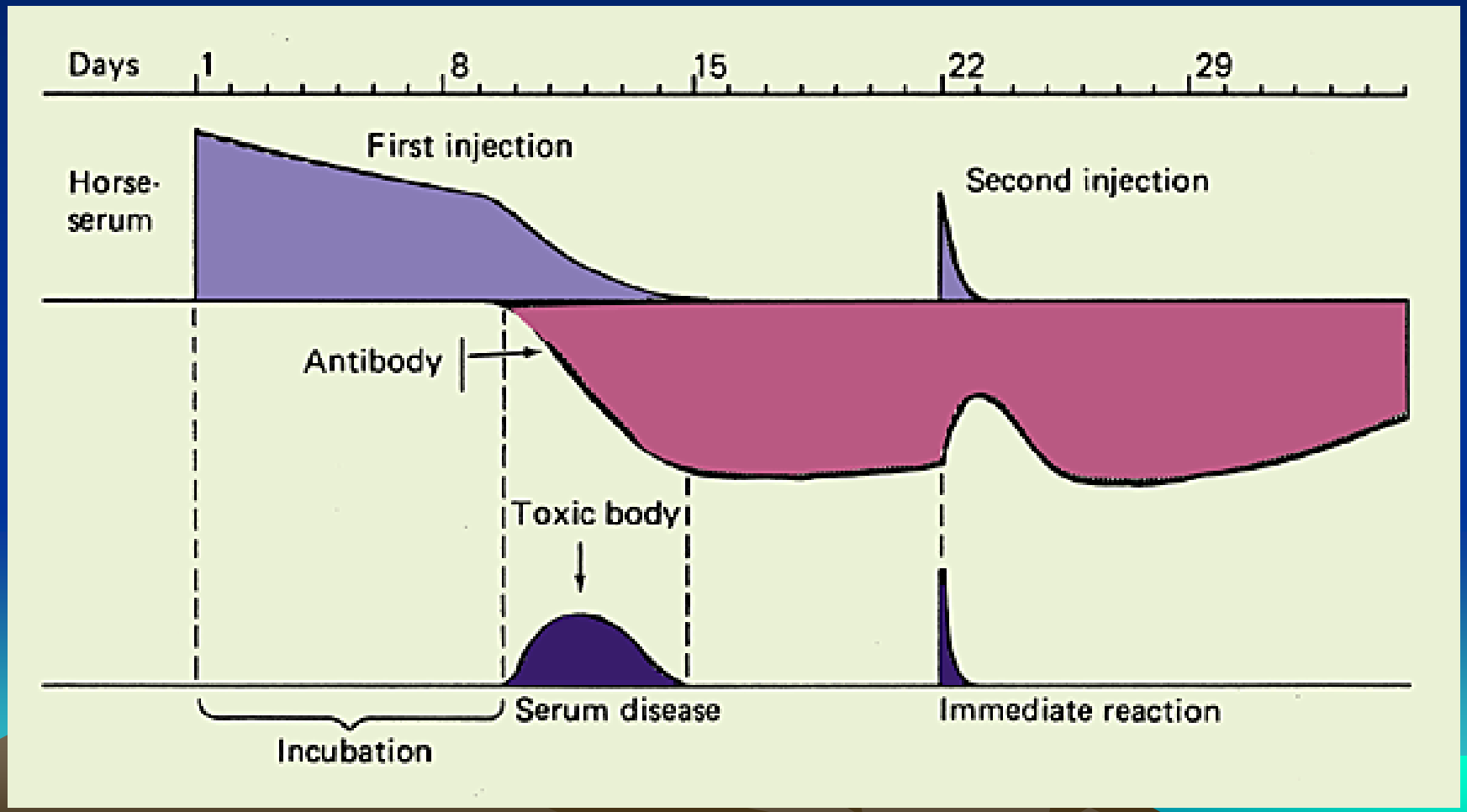
Reporta from Israel, Argentina,India, England, USA

When Evaluating an Adult Patient with the Chronic Urticaria "Syndrome" Consider…

- Physical factors- environmental heat, intense cold, sunlight, vibration or pressure, bath water("Aquagenic" Urticaria).
  - Exercising after eating certain foods such as wheat, celery and shellfish might provoke delayed urticaria.
  - Dermatographism it indicates just how easily they can release histamine in the skin. Can be diagnose by holding a block of ice against the skin for 5 minutes and see if an urticaria wheal develops after the ice is removed.

- Chronic undetected dental, sinus, urinary or parasitic *infections*
- *Stress* is known to aggravate urticaria. Stress reduction measures are very important in treating chronic urticaria.

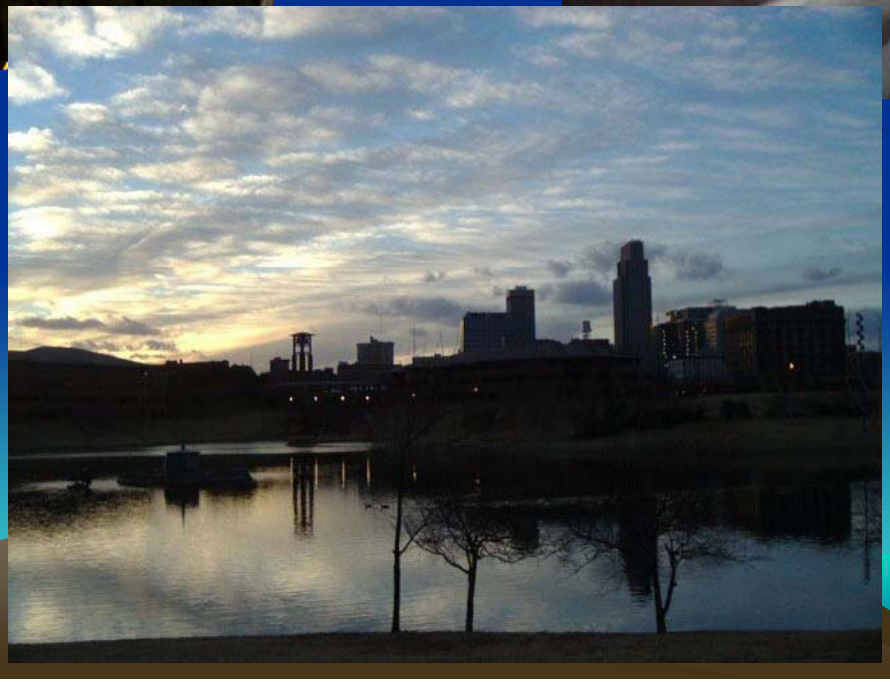
Clemens Freiherr von Pirquet: Explaining immune complex disease in 1906



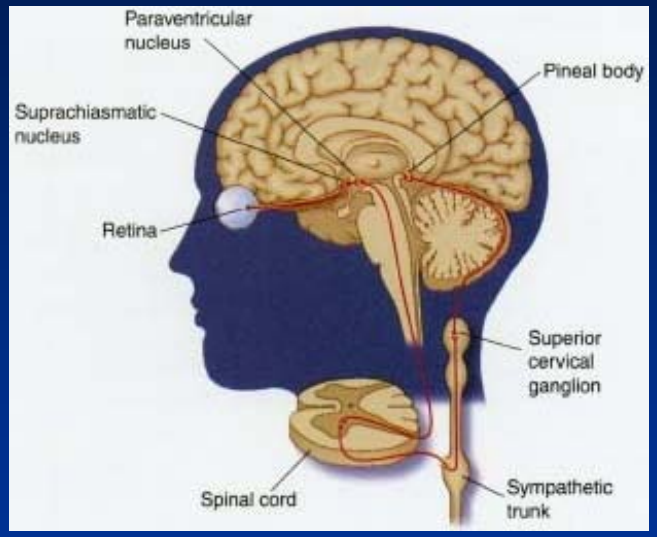
When Evaluating an Adult Patient with the Chronic Urticaria "Syndrome" Consider…(cont)

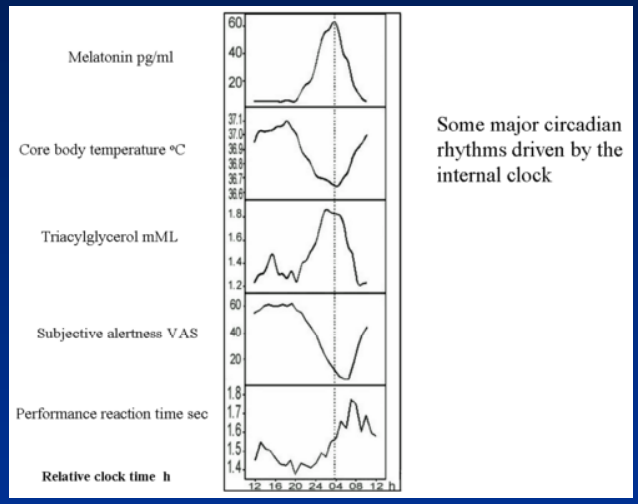
- Allergy to foods, preservatives, or food coloring agents. Consider wheals and swelling developing during the next hours after food ingestion, recent change in diet or ingestion of processed foods
- Medication usage: new medication or supplement started or dosage changed (prescription or over-the-counter, particularly aspirin, NSAIDs).
- ACE inhibitor blood pressure pills play a very important role

The “twilight” or “nightfall” Effect

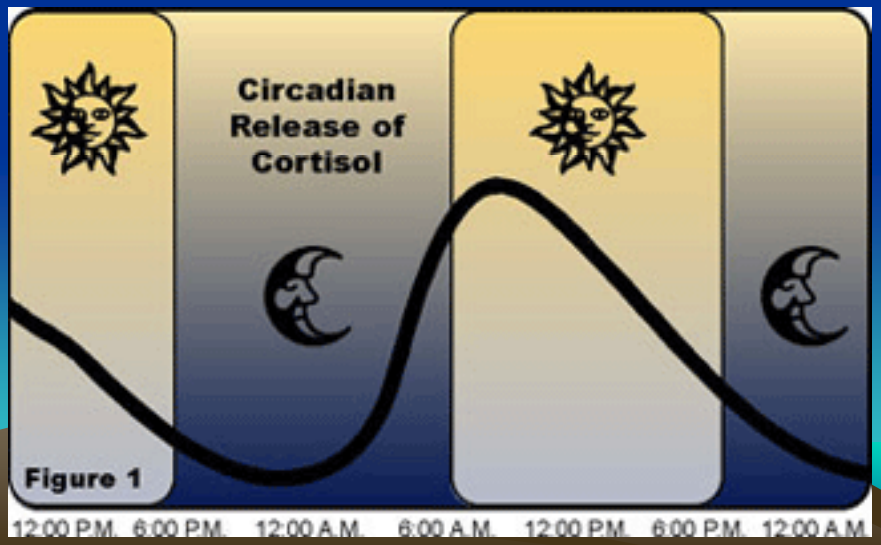


Circadian Rhythm

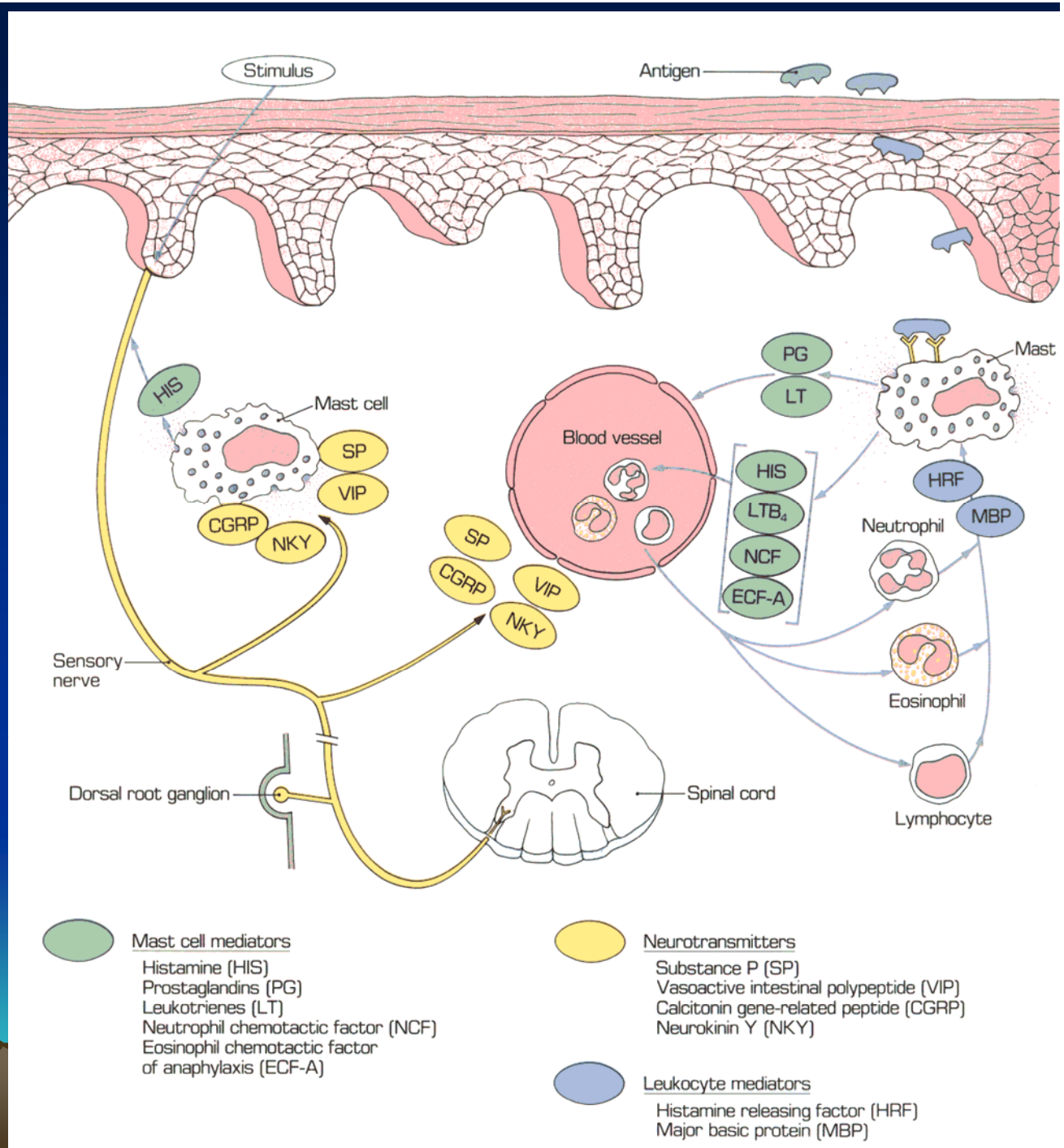




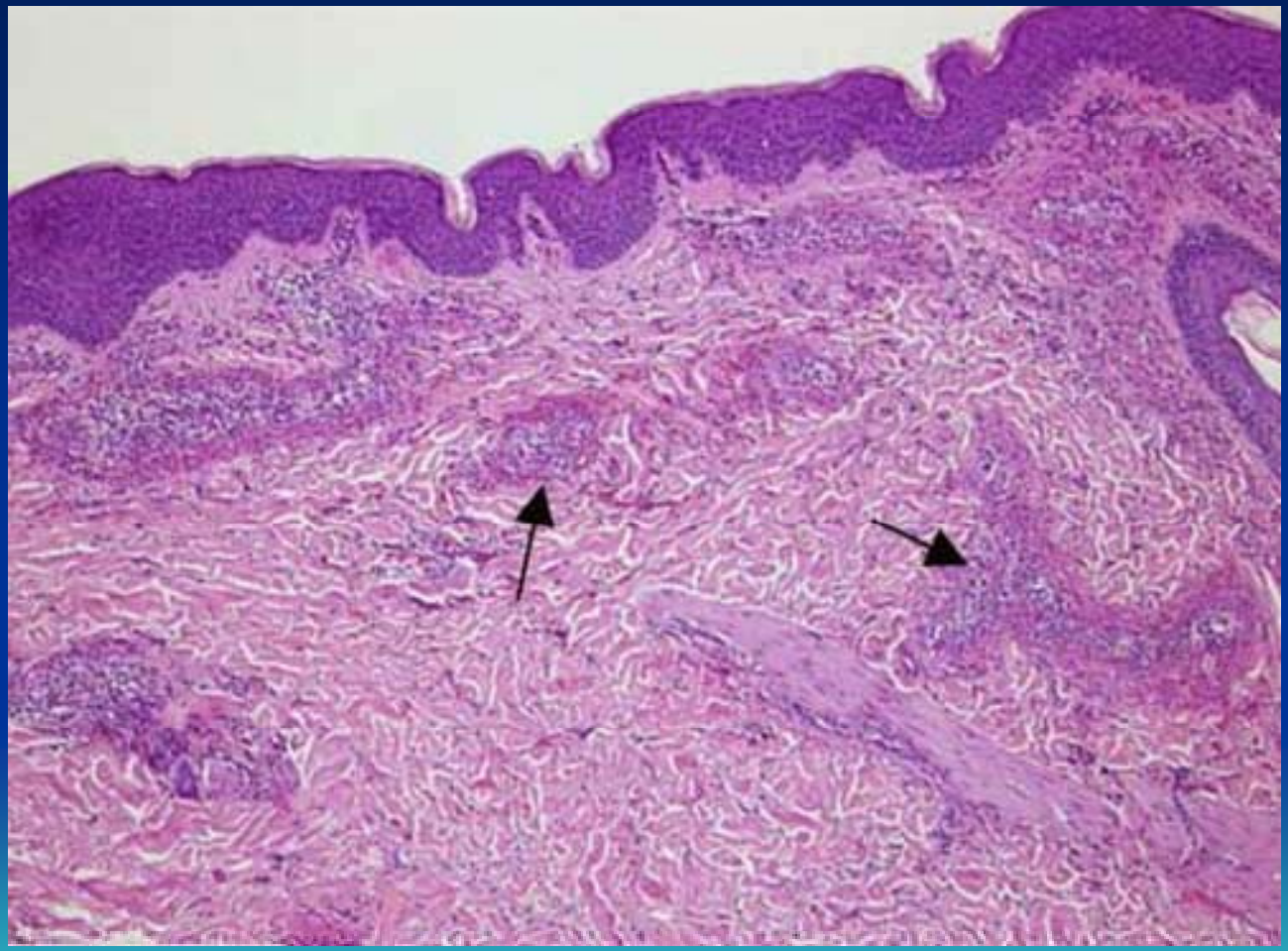
Some major circadian rhythms driven by the internal clock



Role of Neuropeptids in the pathogenesis of Chronic Urticaria



Vasculitis biopsy



Value of Skin Biopsy in Chronic Urticaria (CU)

- Prospective chart review, 43 patients, 10 males, 2001-06
- Predominant cells-

  5-neutrophiles
  9-combined neut and eosin
  6-no predominant cells
  11-eosinophiles
  12-lymphocytic

- 71% with neutrophilic with or withuot eosinphiles required steroids or other immunomodulator as compare to…
- Only 18% of eosinophilic, 58% of lymphocytic or 33% of no defined predominance required steroids

B Kim, et al, Winthrop Unv Hosp, NY, AAAAI Meeting, 03-08

How do we treat urticaria?

- Avoid any obvious triggers or exacerbating factors and try these simple measures:
  - Keep the skin cool, avoid getting hot from exercise and take lukewarm baths. Resist to rub the itchy skin.
  - Apply copious amounts of moisturising creams to reduce dryness and itch.
  - Avoid alcoholic drinks and foods containing additives (sodium benzoate, sulphite, colourings and salicylate, ?)
  - Apply 1% menthol in aqueous cream to soothe the affected skin.

Treatment-
General Considerations

- Physical urticarias-exercise, sun, cold, heat, water, pressure and vibration exposure
- Always consider occupational exposure: latex products, chemical irritants (particularly formaldehyde)

Urticaria
Treat Associated Conditions

- Allergy
  - Elimination diet and other avoidance measures
  - Immunotherapy (?)
- Autoimmune disease
  - Thyroiditis, RA, SLE, Vasculitis
- Malignancy (lymphomas, breast, GI, prostate)
- Infections
  - Travel out of country, exposure to disease (parasitic, fungal, bacterial, or viral infection)

Treatment-
Consider Medications Side Effects

- Avoid medications
  - Including aspirin or codeine containing medication.
  - Avoid ACE inhibitor blood pressure pills (lisinopril, ramipril, enalapril & perindopril).
  - Carefully read Side Effects list

Urticaria-
Pregnancy Considerations

Antihistamine Use During Pregnancy and Selected Birth Defects

- Pregnancy may specifically aggravate urticaria.

- No antihistamines labeled to date meet the FDA requirement for pregnancy category A
  - Most antihistamines classified in pregnancy category B or C
- Of 514 comparisons made (14 antihistamines X 39 birth defects)
  - 31% (n=168) had at least 5 exposed cases available for analysis

Gilboa SM*, Olshan AF, Werler MM, Correa A, and the National Birth Defects Prevention Study
National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

Urticaria-
Pregnancy Considerations

Antihistamine Use During Pregnancy and Selected Birth Defects

- Prevalence of antihistamine use consistent with the literature
- Limited evidence of association between antihistamine use and selected birth defects
- No statistically significant associations for:
  - Cetirizine
  - Dimenhydrinate
  - Hydroxyzine
  - Promethazine
  - Antihistamine NOS
  - Clemastine
  - Fexofenadine
  - Loratadine
  - Triprolidine

Gilboa SM*, Olshan AF, Werler MM, Correa A, and the National Birth Defects Prevention Study
National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

Urticaria-
Pregnancy Considerations

- Safe in pregnancy and breast feeding
  - Decongestants
  - Topical steroids and antihistamines
  - Some antibiotics
  - Bronchodilators
  - Oral steroids

Results (with at least 5 exposed cases)

- **Any antihistamine associations**
  - Spina bifida: (aOR = 1.46 ; 95% CI = 1.05, 2.02)
  - Intestinal atresia: (aOR = 1.78 ; 95% CI = 1.10, 2.88)
  - Transverse limb reductions: (aOR = 1.49 ; 95% CI = 1.04, 2.15)

- **Diphenhydramine associations**
  - Spina bifida: (aOR = 2.19 ; 95% CI = 1.12, 4.28)
  - Hydrocephaly: (aOR = 3.64; 95% CI = 1.58, 8.37)
  - RVOTO: (aOR = 2.23; 95% CI = 1.20, 4.14)
  - Cleft lip w/wo cleft palate: (aOR = 1.86; 95% CI = 1.63, 3.00)
  - Craniosynostosis: (aOR = 2.86; 95% CI = 1.55, 5.25)
  - Gastroschisis: (aOR = 2.64; 95% CI = 1.26, 5.56)

Results (with at least 5 exposed cases)

- **Doxylamine associations**
  - Spina bifida: (aOR = 2.28; 95% CI = 1.17, 4.43)
  - HLHS: (aOR = 3.94; 95% CI = 1.91, 8.11)
- **Meclizine association (5 exposed cases/1 exposed control)**
  - Cleft palate (aOR = 30.72; 95% CI = 3.49, 270.67)
- **Pheniramine association**
  - Cleft lip w/wo cleft palate (aOR = 1.68; 95% CI = 1.12, 2.51)

Urticaria Treatment- Antihistamines

- The mainstay of treatment is high dose (second generation/less sedating) **ANTIHISTAMINE** medication which may be necessary for prolonged periods.
- Add H2 type of antihistamines or "stomach-ulcer treatment“
- Occasionally we need to add sedating antihistamines.

Urticaria Treatment- Antileukotrienes, Doxepin, Steroids

- Newer leukotriene receptor antagonists - have provided some symptom relief, in some patients, when used in combination with antihistamines.
- Oral Doxepin.
- Short courses of oral steroids may be necessary for short periods to settle more severe symptoms.
  - Careful when used for prolonged periods of time as this may lead to glaucoma and osteoporosis in adults.
  - QOD better than daily use! Orally better than parenterally!

Urticaria-Emotional Factors

- Emotional factors: Psychological factors are reported to play a role in a number of patients. Reports exist of improvement of symptoms using hypnotism; however, the role of emotional factors remains controversial.

IV Ig in Chronic Urticaria

- 3 patients with autoimmune urticaria (CAU)
- Failed antihistamine, antileukotriene, hydroxychloroquine, sulfasalazyne, dapsone, colchicine, cyclosporine
- Improvement with IVIg 400g or 1Gm /kg/day for 4 days
- Improvement in all, no side effects

SM Asmar, et al, Nat Jewish, AAAAi Meeting 2008

Treatment

- Highly specialised third line treatments may include Immunosuppressive drugs
  - Ciclosporin, Methotrexate, and Sulphasalazine, Androgen hormones, Nifedipine and Warfarin.
  - Colchicine and Dapsone are useful in treating Urticarial Vasculitis.
  - If available, Immunoglobulin injections,
  - Plasmapheresis or the use of novel anti-IgE monoclonal antibodies such as
    - Omalizumab may be necessary.

- The future holds many exciting new therapeutic modalities including DNA Plasmid Vaccines.

•**Reference:** Powell RJ, du Toit GL, Siddique N et al,
• BSACI guidelines for the management of chronic urticaria and angio-oedema.
•Clin Exp Allergy 2007: 37; 631-650.

Nature and Nurture Concept