Allergy & Urticaria

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Conflict of Interest Disclosures

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None

Objectives

Upon completion of this lecture the participant should be able to:

- Identify the differential diagnosis of urticaria and angioedema
- Explain the appropriate laboratory evaluation of urticaria and angioedema
- Describe the conventional treatment approach for urticaria and angioedema

Definitions

- Urticaria
  - erythematous, well circumscribed wheals
  - dilated blood vessels & edema in *superficial* dermis
- Angioedema
  - well-demarcated, often painful, swelling of skin
  - dilated blood vessels & edema in *deep* dermis
  - distinguish from hydrostatic edema
    - nondependent, asymmetric & transient

Pathophysiologic Classification

- IgE dependent (mast cell - histamine)
  - drug, food, insect, idiopathic
- Direct mast cell releasing agents
  - radiocontrast media, vancomycin, opiates
- Kinin-mediated
  - hereditary angioedema (HANE), ACE inhibitors
- Altered arachidonic acid metabolism
  - ASA, NSAIDS
- Idiopathic (autoimmune)

Histopathology

- Edema
  - Widening of dermal papillae, flattening of rete pegs, swelling of collagen fibers
- Cellular infiltrate
  - Rare in acute urticarial lesions
  - Chronic urticaria
    - non-necrotizing, perivascular infiltrate
    - predominance of mononuclear cells
    - occasional granulocytes
    - increasing number of degrandulated mast cells

Temporal Features

- Acute vs chronic urticaria
  - *Acute*: < 6 weeks duration
    - peak incidence: childhood & early adulthood
    - cause found 15-20% of cases
  - *Chronic*: > 6 weeks duration
    - peak in 30's – 40's
    - female >> male
    - cause elusive (< 5% of cases)

Demographics

- 10-25% of population experience urticaria
- 25% of hives last >6 weeks (chronic)
- In patients with chronic urticaria
  - 50% persist for 3 - 12 months
  - 20% persist for 12 -36 months
  - 20% persist for 36 - 60 months
  - 1.5% persist for 20 - 25 years

Acute Urticaria: Etiologic Classification

- Drug allergy
- Food allergy
- Latex allergy
- Insect sting allergy
- Inhalant allergens (e.g cat dander)
- Contactant allergens (e.g nettle)
- Transfusion reaction
- Viral infections

Drug Allergy

- Urticaria/angioedema may occur with any drug
- Seen most commonly with:
  - antibiotics, NSAIDS, proteins or serums
- Acute, self-limited urticaria
- Resolves with discontinuation of the offending agent

Case Report

- 55 yo woman swelling of tongue
- Began after eating:
  - beef steak, mashed potatoes & peas (self-prepared)
    - eaten previously without reaction
- PMH/ROS:
  - HBP on therapy with lisinopril (for > 6 months)
    - no previous history of adverse reactions
  - No prior history of allergic disease
    - no asthma, rhinitis, food or drug intolerances

Case Questions

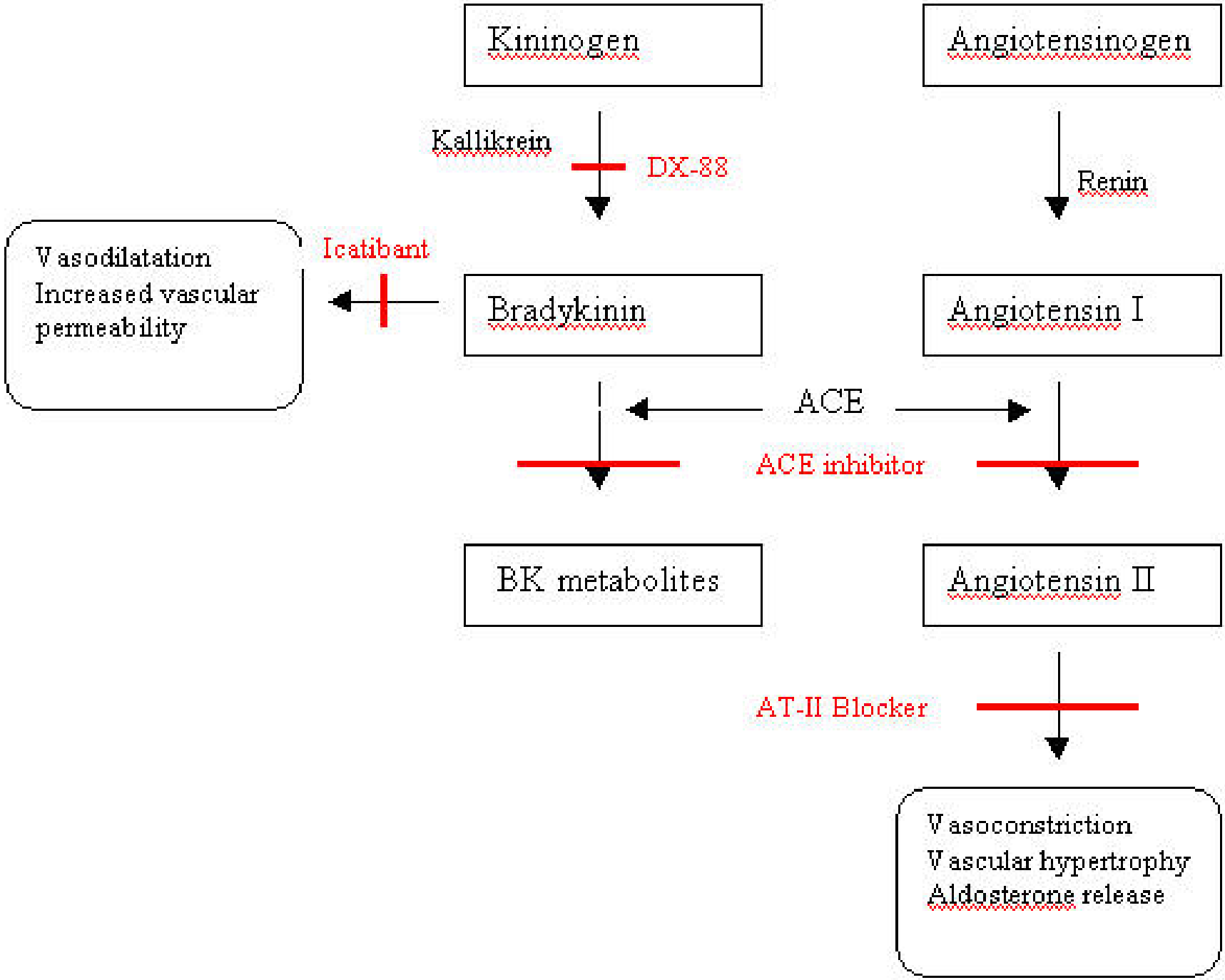
- What is most likely cause of swelling?
- True statements about ACE inhibitors include:
  - ACE inhibitor-induced angioedema is unlikely to begin after 4 weeks of drug therapy
  - Pts with reaction to ACE inhibitors are likely to tolerate other ACE inhibitors
  - ACE induced angioedema has a predilection for the head and neck
  - Angioedema has NOT been reported with ACE II blockers (i.e. receptor antagonists)

Case Answers

- What is most likely cause of swelling?
  - ACE inhibitor: lisinopril
- True statements about ACE inhibitors include:
  - ACE inhibitor-induced angioedema is unlikely to begin after 4 weeks of drug therapy
  - Pts with reaction to ACE inhibitors are likely to tolerate other ACE inhibitors
  - ACE induced angioedema has a predilection for the head and neck
  - Angioedema has NOT been reported with ACE II blockers (i.e. receptor antagonists)

ACE Inhibitor Induced Angioedema

- Incidence of angioedema: 0.1 – 0.7%
- Idiosyncratic reaction
- Predilection for the head & neck
- Onset:
  - most often in first week of treatment
  - may be delayed for months - years
- Mechanism: disruption of the bradykinin degradation pathway


Kininogen
Angiotensinogen
Kallikrein
DX-88
Renin
Vasodilatation
Increased vascular permeability
Icatibant
Bradykinin
Angiotensin I
ACE
ACE inhibitor
BK metabolites
Angiotensin II
AT-II Blocker
Vasoconstriction
Vascular hypertrophy
Aldosterone release

Drug Allergy: ACE Inhibitors

- Treatment Recommendations
  - Manage the airway
  - Antihistamines, steroids, epinephrine: ? helpful
  - Case reports: fresh frozen plasma*
  - ? Role of newer agents for hereditary angioedema
  - Caution: ACE inhibitors in pts with hx of angioedema
  - Do not substitute other drugs from this class
  - Caution with ACE receptor antagonist class

*JACI 109(2); 370; Ann. Allergy 92(5) 573

Case

- 58 yo male teacher, hx of allergic rx to shrimp, ate stir-fried chicken at local Chinese restaurant
  - immediately has diffuse urticaria
  - wheezing, nausea with abdominal pain
- In ER, responds to epi, antihistamines and IV steroids

Case Questions

- What is the most likely cause of the rx?
  - Shrimp protein allergy
  - Peanut allergy
  - Latex allergy
  - MSG
  - Idiopathic anaphylaxis
- How can you confirm the diagnosis?

Case 2: Answers

- Cause of reaction
  - Answer: Shrimp protein contamination
- How do you confirm diagnosis?
  - Answer: Food skin / RAST tests

Acute Allergy

- Food Allergy
  - Most commonly perceived cause of urticaria
  - IgE – mediated
  - Common cause of acute urticaria
    - ***rarely*** cause of chronic
  - Food dyes/additives seldom cause
  - Food ST & elimination diets rarely help to identify the cause of chronic urticaria

Case

- 24 yo female hospital worker rushed to ER for anaphylactic reaction
- Hx of itching & hives on hands after using latex gloves
- Exposed to gluteraldehyde at work
  - used as an anti-septic
- Day of rx sustained burn to left finger before donning gloves
- PMH: SAR with allergic conjunctivitis

Case Questions

- What test would you order?
  - ST with latex glove extract?
  - Patch test for rubber chemical accelerators?
  - Direct challenge with latex gloves?
  - RAST test for specific IgE antibodies to latex?

Case Answers

- What test would you order?
  - ST with latex glove extract?
  - Patch test for rubber chemical accelerators?
  - Direct challenge with latex gloves?
  - RAST test for specific IgE antibodies to latex?

Acute Allergy

- Latex Allergy
  - Occupationally-associated hives & angioedema
  - Sensitization to proteins in natural rubber
    - results in IgE anti-latex antibodies
  - Contact urticaria is most common symptom
  - May progress to inhalant sensitization
  - Anaphylaxis & death are reported with mucosal &/or parenteral exposure
    - e.g. barium enemas, dental dams

Case (cont)

- Further questioning reveals nausea & hives after eating avocados & bananas
- Would you order additional testing?
  - If so what?
- What specific management issues should be addressed with this patient?

Case Answers

- RAST tests to suspect foods
  - frequent x-reaction with bananas, chestnuts, kiwi fruit and avocados
- Management issues
  - strict avoidance
  - Epi-pen, Medic-Alert bracelet
  - use of non-latex gloves
- Prevention for non-sensitized medical personnel
  - use of non-powdered gloves

Case

"The principal of a Worcester school died Tuesday after being stung by a bee or wasp while playing golf. FS, principal of Nelson Place School & a 36 yr veteran of the city's public schools, was scheduled to retire Sept. 7- his 59th birthday. On Monday, FS was looking for his friend's ball in the bushes on the fifth hole at Leicester CC when he was stung on the legs and eyelid.

Case (cont)

FS was allergic to bee stings, his friend said. ‘He always carried Benadryl in his bag because he had been stung before & had a mild reaction.’ He took his medication but collapsed shortly afterward.”

Case Questions

- If this pt had been seen by you prior to his fatal reaction stating he was “allergic to bees”, what diagnostic and therapeutic steps would you have recommended?

Insect Sting Allergy

- Rx may be local or systemic
- Severe rxs & fatalities more common in adults
  - no fatalities <16yo
- Distinguish biting (mosquitoes) from sting insects
  - ***PAIN!!***
- ST is diagnostic test of choice
- Immunotherapy for systemic reactions only
  - 97% effective
  - seldom necessary <16 yrs old

Insect Sting Allergy

- Management
  - information regarding insect avoidance
  - Medic-Alert bracelet
  - EpiPen
    - need for immediate use
  - Antihistamines
  - Prompt professional emergency care

Chronic and Recurrent Urticaria / Angioedema

Physical Urticarias

Urticarias that occur from physical stimulation of the skin

- Symptomatic dermatographism
- Cold-induced
- Cholinergic urticaria (heat)
- Exercise-induced
- Delayed pressure urticaria
- Solar
- Aquagenic
- Vibratory

Features of Physical Urticaria

Type	Age (yrs)	Clinical Features	Angio-edema	Diagnostic Test
Dermatographism	20-50	Linear lesions	No	Light stroking of skin; + transfer factor
Cold	10-40	Itchy, pale lesions (5% with cryos)	Yes	5-10 minute ice-cube test; + transfer factor
Cholinergic	10-50	Itchy, monomorphic pale or pink lesions	Yes	Exercise or hot shower; + transfer factor
Pressure	20-50	Large painful or itchy lesions	No	Dermographometer; application of pressure to skin or Sand bag test 15 lb weight for 15 minutes
Solar	20-50	Itchy pale or red swelling	Yes	Irradiation by a solar simulator;+ transfer factor

Chronic urticaria

As a sign of systemic illness

- Infections: bacterial, fungal, viral, helminthes
- Connective tissue diseases
- Malignancy
- Thyroid disease
- C1 inhibitor deficiencies
- Urticaria pigmentosa / mastocytosis
- Chronic urticaria as an autoimmune disease

Infection

- Viral infections
  - Childhood respiratory and gastrointestinal infections
  - Infectious hepatitis (Hep. A, B and C)
  - Mononucleosis
- Undetected bacterial infections
  - Anecdotal reports (e.g. dental abscess)
- Parasites: Helminthes
- Lyme disease
- ? H.pylori

Connective Tissue Disease

- Disorders associated with urticaria
  - SLE, cryoglobulinemia, urticarial vasculitis, serum sickness, Sjogren
- Caused by an immune-complex mediated mechanism
- May have associated cutaneous vasculitis

Urticaria with Vasculitis

- Diagnostic features of lesions:
  - last longer than 24 hrs
  - more prominent on lower extremity
  - have purpuric component
  - leave hemosiderin pigment after resolving
  - associated with systemic symptoms
    - fever, arthralgia/arthritis, GI & resp. symptoms

Urticarial Vasculitis: Features That Differentiate It From CIU

Feature	Chronic urticaria	Urticarial vasculitis
Wheal duration	<24 hr	>24 hr (not always true)
Purpura/pain/hyper-pigmentation	No	Yes
Systemic signs	Usually none	Yes
Laboratory findings	Usually normal	Increased WSR, Acute Phase Reactants; Decreased C3/C4
Leukocytoclasia or extravasation of RBCs	No	Yes
Response to antihistamines	Yes	Sometimes

Malignancy

- Case reports of occurrence with:
  - CA of colon, rectum, lung & breast
- Relationship has NOT been firmly established
- *Lindelof et al (BMJ 1990)*
  - 1155 consecutive cases of chronic urticaria
    - 36 diagnosed with cancer
    - 41 expected based on standard incidence data
- W/U for malignancy based on history & PE

Thyroid Disease

- *Lenznoff et al (1989) JACI*
  - 90/624 (14.4%) CU have thyroid autoantibodies
    - 7:1 female: male
  - 44/90 (48%) had previously undetected thyroid disease
  - ~ 5.6% of controls have positive antibodies
- Worthwhile to look for autoimmune thyroid disease in chronic urticaria

Case Report

- 40 yo female with long standing hx. Of monthly episodes of abdominal pain
  - lasts 2-3 days
  - not relieved by antacids or H_2 blockers
- She also gets episodic swelling of the hands and face
  - no urticaria
  - lasts 3-7 days
  - does not respond to antihistamines, steroids or epinephrine
- No medications; no allergies

Case Questions

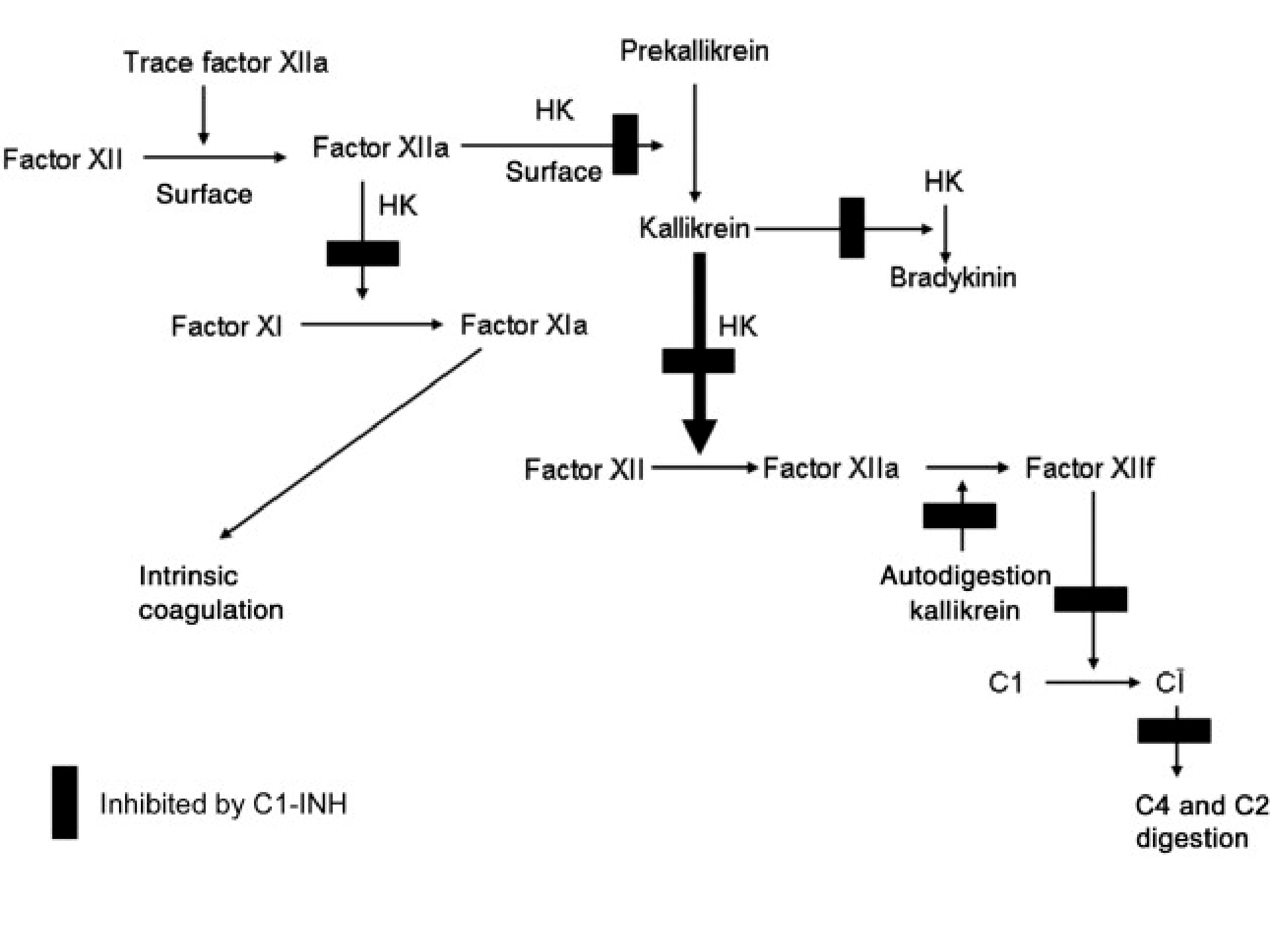
- What screening serologic test would you perform?
  - Serum C4
  - Serum C2
  - ESR
  - Serum kinin
  - ANA
- What definitive test would you perform?

C1 inhibitor deficiency

C1 INH is a serine protease inhibitor

Regulates complement, coagulation & kinin-forming systems

Deficiency may be either hereditary or acquired


Trace factor XIIa
Prekallikrein
HK
Factor XII
Factor XIIa
Surface
Surface
HK
HK
Kallikrein
Bradykinin
Factor XI
Factor XIa
HK
Factor XII
Factor XIIa
Factor XIIf
Intrinsic
coagulation
Autodigestion
kallikrein
C1
C1
C4 and C2
digestion
Inhibited by C1-INH

Hereditary angioedema

- Autosomal dominant
- Worldwide incidence estimated from 1:10,000 to 1:150,000

- Type 1 (85%): diminished protein production
- Type 2 (15%): normal protein level but defective function

- Screening test: C4 complement level
- Confirmatory test: C1INH level and function

Acquired C1INH deficiency

Type I: Lymphoproliferative Disease

- Benign MGUS
- B cell lymphoma
- Multiple Myeloma
- CLL

Type II: Antibodies to C1 Inhibitor

- Infections
- Autoimmune diseases
- Idiopathic (14%)

Older age of onset than HAE

Complement Profiles in Angioedema

	C1 INH	C1 INH Funct.	C1q	C4
Type I HAE	↓	↓	N	↓
Type II HAE	N	↓	N	↓
Acq Type I	↓	↓	↓	↓
Acq Type II	↓	↓	↓	↓
Idiopathic	N	N	N	N

Therapies for C1 inhibitor Deficiency

- Anabolic steroids
- Anti-fibrinolytics
- FFP

- Plasma derived C1 inhibitor (Cinryze)
- Recombinant C1 inhibitor (Rhucin)
- Kallikrein inhibitor (Ecallantide)
- BK2R antagonist (Icatibant)

Mastocytosis

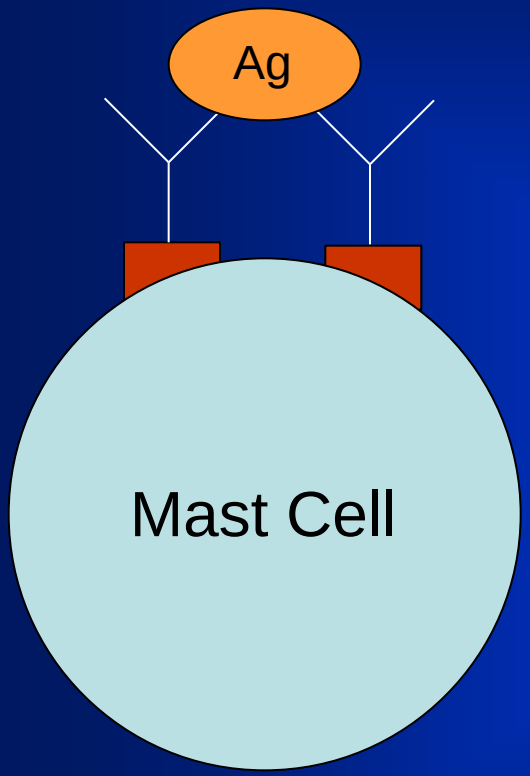
- Indolent disease
  - urticaria pigmentosa
  - syncope
  - ulcer disease, malabsorption
  - BM mast cell aggregates, skeletal disease
  - hepatosplenomegaly
  - Lymphadenopathy
- Associated Hematologic disorders
  - myeloproliferative, myelodysplastic disease
- Aggressive mastocytosis with eosinophilia
- Mast cell leukemia

Chronic Urticaria as an Autoimmune Disease

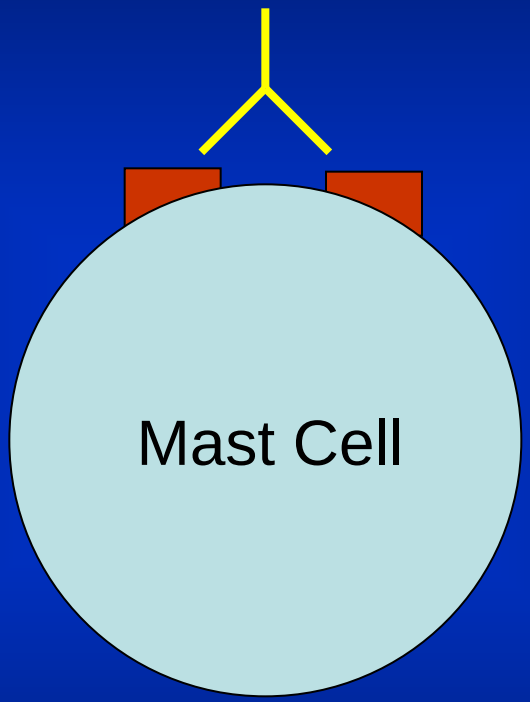
- 1980's – Identification of a wheal-producing factor in the serum of some pts with CIU

- IgG autoantibody directed against either:
  - the high affinity Fc receptor of IgE (FcεRI)
  - IgE

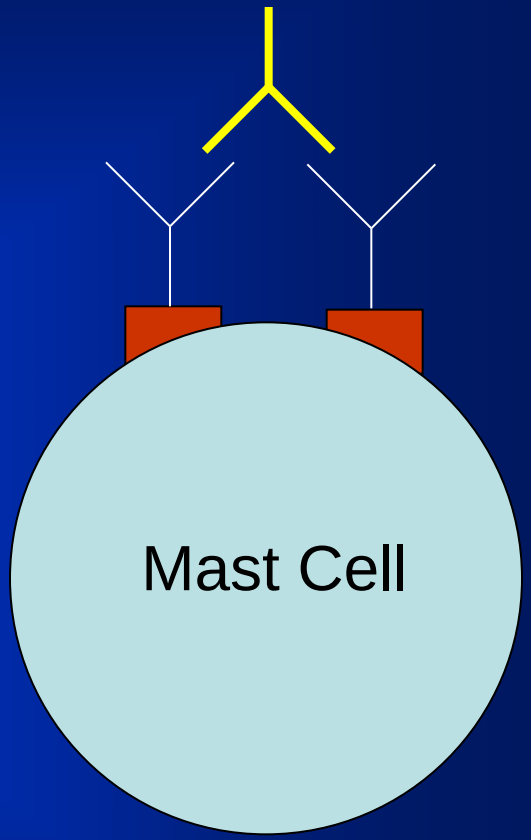
Hide et al (1993) *NEJM*
Fiebiger et al (1996) *J Clin Invest*



Antigen



Anti-FcεRI



Anti-IgE

Summary: Autoantibodies in CIU

- Anti-FcεRI Abs are present in 30-40% CIU
- Functional autp-antibodies accounts for histamine release → uritcaria/angioedema
- Other unidentified histamine releasing factors exists in CIU

Chronic Urticaria

- ~90% of urticaria is “idiopathic”
- 2:1 female:male
- rarely life-threatening, often disabling
- often resistant to conventional treatment

Case 6: Further Questions

- What is a reasonable investigative w/u for CIU?

Laboratory Evaluation

- Routine evaluation:

There is no consensus regarding the appropriate tests which should routinely be performed for patients with CU without atypical features by history or physical exam.

Evaluation of CU/Angioedema

- Commonly performed tests are:
  - CBC with differential
  - Sedimentation rate and/or C-reactive protein.
- Some clinicians routinely perform:
  - Chemistry panel
  - Hepatic panel
  - TSH
  - Anti-microsomal antibodies, anti-thyroglobulin antibodies

- Further lab testing to R/O diagnoses suggested by H&P

Evaluation of CIU/Angioedema

In Selected Patients:

- CBC /. ESR
- Chem profile
- ANA
- Hepatitis B or C testing
- Cryoproteins
- C4, C1INH
- Stool O&P
- ST for IgE mediated rx
- RAST for specific IgE
- Skin biopsy
- Circulating immune complexes
- Lyme serology
- H.pylori

Diagnostic Testing in CU

- **SUMMARY STATEMENT 29:** After a thorough history and physical examination, **no diagnostic testing may be appropriate** for some patients with CU; however, **limited routine lab testing may be performed** to exclude underlying causes. Targeted lab testing based on clinical suspicion is appropriate. **Extensive routine testing** for exogenous and rare causes of CU, or immediate hypersensitivity skin testing for inhalants or foods, is **not warranted.** Routine laboratory testing in patients with CU, whose history and physical examination lacks atypical features, rarely yields clinically significant findings.[C]

Management

- Avoid or remove inciting agents or triggers
  - e.g. drugs, foods
- Treat underlying illness
- Medications
  - Antihistamines
  - Corticosteroids
  - Others

Antihistamines

- First generation H_1 antagonists
  - Chlorpheniramine, diphenhydramine, hydroxyzine , cyproheptadine
- Second-generation H_1 antagonists
  - Claritin (loratadine), Allegra (fexofenadine), Zyrtec (cetirizine),
  - Clarinex (desloratadine), Xyzal (levocetirizine)
- Sinequan (Doxepin)

High Dose Antihistamines in CU

- Cetirizine: conflicting studies
- Fexofenadine: no difference between 60 mg, 120 mg and 240 mg twice a day
- Desloratadine
  - 20 mg > 5 mg in cold urticaria
- Levocetirizine and desloratadine
  - Higher doses better

* *These are off-label recommendations*

Kavosh ER, Khan DA. Am J Clin Dermatol 2011 Dec 1;12(6):361-76.

Antihistamines

- ~15% of cutaneous histamine receptors are H_2 receptors
- If H_1 is adequately blocked, adding H_2 may be helpful
- **H_2** antagonists
  - Tagamet (cimetidine), Zantac (ranitidine), Pepcid (famotidine), Axid (nizatidine)

Systemic Corticosteroids in CU

- Systemic corticosteroids are frequently used in patients with CU refractory to antihistamine therapy
- No controlled trials have demonstrated the efficacy of systemic corticosteroids in CU
- “systemic corticosteroids should be avoided for long-term treatment of CU, since dosages necessary to suppress symptoms are usually high with significant adverse effects” (International Consensus Meeting on Urticaria)

Allergy 2009;64:1427-43.

Alternative Agents in Urticaria

- Alternative agents for CU are therapies used for patients failing conventional (i.e. antihistamine) therapy
- Alternative agents have a variety of mechanisms
    - Antiinflammatory
    - Immunosuppressant
    - Immunomodulatory
    - other

Leukotriene antagonists

- Anecdotal reports of efficacy
- Studies:
  - 3 studies claim efficacy
  - 1 study is negative
- Well tolerated, few side effects

- Receptor Antagonists
  - Accolate (zafirlukast) 20 mg b.i.d.
  - Singulair (montelukast) 10 mg daily
- Synthesis Inhibitor
  - Zyflo (zileuton) 600 mg 2-4 times daily

TABLE 12-1—Evidence for Therapies in Chronic Urticaria

Drug	Level of Evidence	Quality & Amount of Evidence	Potential for Serious Adverse Effects	Cost
H1 antihistamines	Ia	High	Low	Low
H2 antihistamines	Ib	Low	Low	Low
doxepin	Ib	Moderate	Low	Low
Systemic corticosteroids	IV	Low	High	Low
Leukotriene modifiers	Ib	Moderate	Low	Moderate
dapsone	IIb	Low	Moderate	Low*
sulfasalazine	III	Low	Moderate	Low*
hydroxychloroquine	Ib	Low	Low	Low
colchicine	III	Low	Low	Low
Calcineurin inhibitors	Ib	Moderate	High	High*
mycophenolate	IIb	Low	Moderate	High*
omalizumab	Ib	Low	Moderate	High
IVIG	IIb	Low	Moderate	High*
Beta-agonists	Ib (no effect) III (effect)	Moderate Low	Moderate	Low
NSAIDs	III	Low	Moderate	Low
Methylxanthines	Ib	Moderate	Moderate	Low*
Phototherapy	Ib	Moderate	Moderate	High
Androgens	Ib	Low	Moderate	Moderate*
Methotrexate	III	Low	High	Low*
Anticoagulants	III	Low	High	Low*

Khan DA. In: Maibach HI, Gorouhi F ed. Evidence Based Dermatology 2nd ed. 2011

Omalizumab (anti-IgE) for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

Marcus Maurer, M.D., Karin Rosén, M.D., Ph.D., Hsin-Ju Hsieh, Ph.D., Sarbjit Saini, M.D., Clive Grattan, M.D., Ana Gimenéz-Arnau, M.D., Ph.D., Sunil Agarwal, M.D., Ramona Doyle, M.D., Janice Canvin, M.D., Allen Kaplan, M.D., and Thomas Casale, M.D.

N Engl J Med 2013; 368:924-935; March 7, 2013

Conclusions

Omalizumab diminished clinical symptoms and signs of chronic idiopathic urticaria in patients who had remained symptomatic despite the use of approved doses of H1-antihistamines. **Conclusions**

Future

- Continued characterization of releasing factors
- Commercial ELISA for anti-FcεRI
- New treatment modalities
  - stabilize the mast cell
  - block binding of autoantibody to FcεRI
- Xolair – anti IgE monoclonal antibody